

(26) DNA228201 (TAT116)

The malignant cells of 13/16 colorectal adenocarcinomas are positive for TAT116 expression. Additionally, 9/10 metastatic adenocarcinomas are positive for expression. Expression is also observed in the basal portions of normal colonic crypts.

(27) DNA247488 (TAT189)

The malignant cells of 13/16 colorectal adenocarcinomas are positive for TAT189 expression. Additionally, 9/10 metastatic adenocarcinomas are positive for expression. Expression is also observed in the basal portions of normal colonic crypts.

(28) DNA236538 (TAT190)

The malignant cells of 13/16 colorectal adenocarcinomas are positive for TAT190 expression. Additionally, 9/10 metastatic adenocarcinomas are positive for expression. Expression is also observed in the basal portions of normal colonic crypts.

(29) DNA247489 (TAT191)

The malignant cells of 13/16 colorectal adenocarcinomas are positive for TAT191 expression. Additionally, 9/10 metastatic adenocarcinomas are positive for expression. Expression is also observed in the basal portions of normal colonic crypts.

(30) DNA228994 (TAT124)

Thirteen of 61 cases of non small cell lung carcinoma are positive for expression of TAT124. Expression level in these positive tumor samples is significantly higher than in normal adult tissues.

(31) DNA231542 (TAT100)

In situ analysis performed as described above evidences significantly upregulated expression in human glioma and glioblastoma tissues as compared to normal brain (and other) tissues.

(32) DNA231542-1 (TAT284)

In situ analysis performed as described above evidences significantly upregulated expression in human glioma and glioblastoma tissues as compared to normal brain (and other) tissues.

(33) DNA231542-2 (TAT285)

In situ analysis performed as described above evidences significantly upregulated expression in human glioma and glioblastoma tissues as compared to normal brain (and other) tissues.

(34) DNA297393 (TAT285-1)

In situ analysis performed as described above evidences significantly upregulated expression in human glioma and glioblastoma tissues as compared to normal brain (and other) tissues.

(35) DNA236534 (TAT102)

Expression of TAT102 is seen in 14 of 15 ovarian epithelial malignancies (adenocarcinoma, epithelial surface tumors, endometrioid Ca). Also, 8 of 9 endometrial adenocarcinomas of the uterus express TAT102. Moreover, expression of TAT102 is seen in 24 of 27 non-small cell lung cancers, positive cases include squamous and adenocarcinomas. Expression in these tumor tissues is significantly higher than in their normal tissue counterparts.

(36) DNA246430 (TAT109)

Fourteen of 92 breast tumor samples are positive for TAT109 expression. Expression in all normal tissues is undetectable.

(37) DNA264454 (TAT106)

Expression of TAT106 is observed in 38/88 breast tumors. Expression in normal breast tissue is weak or undetectable.

(38) DNA98565 (TAT145)

Positive signal for TAT145 was observed in most gliomas, glioblastomas, some melanomas, and normal brain (primarily localized to astrocytes). The signal intensity in the glioblastomas appeared to be greater than that in normal astrocytes. While the majority of glioma and glioblastoma samples tested were positive for TAT145 expression, the majority of normal brain samples tested were negative for such expression.

(39) DNA246435 (TAT152)

Positive signal for TAT152 was observed in most glioblastomas, some melanomas, and normal brain (primarily localized to astrocytes). The signal intensity in the glioblastomas appeared to be greater than that in normal astrocytes. While the majority of glioma and glioblastoma samples tested were positive for TAT152 expression, the majority of normal brain samples tested were negative for such expression.

(40) DNA167234 (TAT130)

Seventy cases of primary adenocarcinoma of the prostate were available for review. Of these 70 cases, 56 cases (80%) are positive for TAT130 expression. TAT130 expression in non-prostatic tissues is weak or undetectable.

(41) DNA235621 (TAT166)

Seventy cases of primary adenocarcinoma of the prostate were available for review. Of these 70 cases, 56 cases (80%) are positive for TAT166 expression. TAT166 expression in non-prostatic tissues is weak or undetectable.

(42) DNA236493 (TAT141)

Positive expression is observed in 70/148 breast carcinomas, 2/63 colorectal adenocarcinomas, 4/42 ovarian tumors, 9/69 non small cell lung carcinomas, 9/67 prostate adenocarcinomas and 5/25 gliomas. Expression in normal non-cancerous tissues appears restricted to prostate and breast epithelium.

(43) DNA226094 (TAT164)

Twenty one of 37 glioblastoma samples and 8 of 8 glioma samples were positive for TAT164 expression while all other tumor and normal tissues examined (including normal brain tissue) were negative.

(44) DNA227578 (TAT165)

Fifteen of 25 glioblastoma samples tested were positive for expression while significantly weaker expression was observed in the normal brain samples tested.

EXAMPLE 5: Immunohistochemistry Analysis

Antibodies against certain TAT polypeptides disclosed herein were prepared and immunohistochemistry analysis was performed as follows. Tissue sections were first fixed for 5 minutes in acetone/ethanol (frozen or paraffin-embedded). The sections were then washed in PBS and then blocked with avidin and biotin (Vector kit) for 10 minutes each followed by a wash in PBS. The sections were then blocked with 10% serum for 20 minutes and then blotted to remove the excess. A primary antibody was then added to the sections at a concentration of 10 μ g/ml for 1 hour and then the sections were washed in PBS. A biotinylated secondary antibody (anti-primary antibody) was then added to the sections for 30 minutes and then the sections were washed with PBS. The sections were then exposed to the reagents of the Vector ABC kit for 30 minutes and then the sections were washed in PBS. The sections were then exposed to Diaminobenzidine (Pierce) for 5 minutes and then washed in PBS. The sections were then counterstained with Mayers hematoxylin, covered with a coverslip and visualized. Immunohistochemistry analysis can also be performed as described in Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989 and Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). The results from these analyses are show below.

(1) DNA26930 (TAT112)

Significantly higher expression was detected in the apical surface of the colonic crypts of colon tumors than on the apical surface of the normal colonic crypts. Additionally, TAT112 was found to be significantly overexpressed in pancreatic adenocarcinoma cells as compared to normal pancreatic cells. Finally, IHC analysis performed as described above evidenced that TAT112 is significantly overexpressed in lung carcinoma as compared to normal lung tissue, non small cell lung carcinoma as compared to normal lung tissue and stomach carcinoma as compared to normal stomach tissue.

(2) DNA226539 (TAT126)

Positive expression is observed in 2/10 uterine adenocarcinomas, 9/17 ovarian adenocarcinomas and 2/20 non small cell lung carcinomas. Using this procedure, expression of TAT126 was not detectable in any normal tissue.

(3) DNA236511 (TAT151)

Positive expression is observed in 2/10 uterine adenocarcinomas, 9/17 ovarian adenocarcinomas and 2/20 non small cell lung carcinomas. Using this procedure, expression of TAT151 was not detectable in any normal tissue.

EXAMPLE 6: Verification and Analysis of Differential TAT Polypeptide Expression by GEPIS

TAT polypeptides which may have been identified as a tumor antigen as described in one or more of the above Examples were analyzed and verified as follows. An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and interesting EST sequences were identified by GEPIS. Gene expression profiling *in silico* (GEPIS) is a bioinformatics tool developed at Genentech, Inc. that characterizes genes of interest for new cancer therapeutic targets. GEPIS takes advantage of large amounts of EST sequence and library information to determine gene expression profiles. GEPIS is

capable of determining the expression profile of a gene based upon its proportional correlation with the number of its occurrences in EST databases, and it works by integrating the LIFESEQ® EST relational database and Genentech proprietary information in a stringent and statistically meaningful way. In this example, GEPIS is used to identify and cross-validate novel tumor antigens, although GEPIS can be configured to perform either very specific analyses or broad screening tasks. For the initial screen, GEPIS is used to identify EST sequences from the LIFESEQ® database that correlate to expression in a particular tissue or tissues of interest (often a tumor tissue of interest). The EST sequences identified in this initial screen (or consensus sequences obtained from aligning multiple related and overlapping EST sequences obtained from the initial screen) were then subjected to a screen intended to identify the presence of at least one transmembrane domain in the encoded protein. Finally, GEPIS was employed to generate a complete tissue expression profile for the various sequences of interest. Using this type of screening bioinformatics, various TAT polypeptides (and their encoding nucleic acid molecules) were identified as being significantly overexpressed in a particular type of cancer or certain cancers as compared to other cancers and/or normal non-cancerous tissues. The rating of GEPIS hits is based upon several criteria including, for example, tissue specificity, tumor specificity and expression level in normal essential and/or normal proliferating tissues. The following is a list of molecules whose tissue expression profile as determined by GEPIS evidences high tissue expression and significant upregulation of expression in a specific tumor or tumors as compared to other tumor(s) and/or normal tissues and optionally relatively low expression in normal essential and/or normal proliferating tissues. As such, the molecules listed below are excellent polypeptide targets for the diagnosis and therapy of cancer in mammals.

	<u>Molecule</u>	<u>upregulation of expression in:</u>	<u>as compared to:</u>
20	DNA77507 (TAT161)	breast tumor	normal breast tissue
	DNA77507 (TAT161)	colon tumor	normal colon tissue
	DNA77507 (TAT161)	lung tumor	normal lung tissue
	DNA77507 (TAT161)	kidney tumor	normal kidney tissue
	DNA77507 (TAT161)	liver tumor	normal liver tissue
25	DNA77507 (TAT161)	ovarian tumor	normal ovarian tissue
	DNA77507 (TAT161)	pancreatic tumor	normal pancreatic tissue
	DNA77507 (TAT161)	rectum tumor	normal rectum tissue
	DNA77507 (TAT161)	skin tumor	normal skin tissue
	DNA77507 (TAT161)	uterine tumor	normal uterine tissue
30	DNA77507 (TAT161)	brain tumor	normal brain tissue
	DNA77507 (TAT161)	soft tissue tumor	normal soft tissue
	DNA77507 (TAT161)	bone tumor	normal bone tissue
	DNA82343 (TAT157)	colon tumor	normal colon tissue
	DNA82343 (TAT157)	ovarian tumor	normal ovarian tissue
35	DNA82343 (TAT157)	stomach tumor	normal stomach tissue
	DNA82343 (TAT157)	thymus tumor	normal thymus tissue
	DNA82343 (TAT157)	small intestine tumor	normal small intestine tissue
	DNA87994 (TAT160)	breast tumor	normal breast tissue
	DNA87994 (TAT160)	pancreatic tumor	normal pancreatic tissue
40	DNA87994 (TAT160)	colon tumor	normal colon tissue
	DNA87994 (TAT160)	esophagus tumor	normal esophagus tissue
	DNA87994 (TAT160)	ovarian tumor	normal ovarian tissue
	DNA87994 (TAT160)	prostate tumor	normal prostate tissue
	DNA88131 (TAT158)	breast tumor	normal breast tissue
45	DNA88131 (TAT158)	colon tumor	normal colon tissue
	DNA88131 (TAT158)	lung tumor	normal lung tissue

	Molecule	upregulation of expression in:	as compared to:
5	DNA88131 (TAT158)	pancreatic tumor	normal pancreatic tissue
	DNA88131 (TAT158)	prostate tumor	normal prostate tissue
	DNA88131 (TAT158)	stomach tumor	normal stomach tissue
	DNA88131 (TAT158)	bladder tumor	normal bladder tissue
	DNA88131 (TAT158)	brain tumor	normal brain tissue
10	DNA95930 (TAT110)	colon tumor	normal colon tissue
	DNA95930 (TAT110)	lung tumor	normal lung tissue
	DNA95930 (TAT110)	prostate tumor	normal prostate tissue
	DNA95930 (TAT110)	endometrial tumor	normal endometrial tissue
	DNA95930 (TAT110)	ovarian tumor	normal ovarian tissue
15	DNA95930 (TAT110)	breast tumor	normal breast tissue
	DNA95930-1 (TAT210)	colon tumor	normal colon tissue
	DNA95930-1 (TAT210)	lung tumor	normal lung tissue
	DNA95930-1 (TAT210)	prostate tumor	normal prostate tissue
	DNA95930-1 (TAT210)	endometrial tumor	normal endometrial tissue
20	DNA95930-1 (TAT210)	ovarian tumor	normal ovarian tissue
	DNA95930-1 (TAT210)	breast tumor	normal breast tissue
	DNA96917 (TAT159)	pancreatic tumor	normal pancreatic tissue
	DNA96917 (TAT159)	lung tumor	normal lung tissue
	DNA96917 (TAT159)	liver tumor	normal liver tissue
25	DNA96917 (TAT159)	prostate tumor	normal prostate tissue
	DNA96930 (TAT112)	breast tumor	normal breast tissue
	DNA96930 (TAT112)	colon tumor	normal colon tissue
	DNA96930 (TAT112)	lung tumor	normal lung tissue
	DNA96930 (TAT112)	ovarian tumor	normal ovarian tissue
30	DNA96930 (TAT112)	pancreatic tumor	normal pancreatic tissue
	DNA96930 (TAT112)	stomach tumor	normal stomach tissue
	DNA96936 (TAT147)	breast tumor	normal breast tissue
	DNA96936 (TAT147)	colon tumor	normal colon tissue
	DNA96936 (TAT147)	prostate tumor	normal prostate tissue
35	DNA96936 (TAT147)	uterine tumor	normal uterine tissue
	DNA98565 (TAT145)	brain tumor	normal brain tissue
	DNA98565 (TAT145)	colon tumor	normal colon tissue
	DNA246435 (TAT152)	brain tumor	normal brain tissue
	DNA246435 (TAT152)	colon tumor	normal colon tissue
40	DNA98591 (TAT162)	colon tumor	normal colon tissue
	DNA98591 (TAT162)	small intestine tumor	normal small intestine tissue
	DNA98591 (TAT162)	ovarian tumor	normal ovarian tissue
	DNA98591 (TAT162)	esophagus tumor	normal esophagus tissue
	DNA108809 (TAT114)	colon tumor	normal colon tissue
45	DNA108809 (TAT114)	lung tumor	normal lung tissue
	DNA108809 (TAT114)	ovarian tumor	normal ovarian tissue
	DNA108809 (TAT114)	brain tumor	normal brain tissue
	DNA143493 (TAT103)	breast tumor	normal breast tissue
	DNA167234 (TAT130)	prostate tumor	normal prostate tissue
50	DNA235621 (TAT160)	prostate tumor	normal prostate tissue
	DNA176766 (TAT132)	kidney tumor	normal kidney tissue
	DNA176766 (TAT132)	uterine tumor	normal uterine tissue
	DNA236463 (TAT150)	kidney tumor	normal kidney tissue
	DNA236463 (TAT150)	uterine tumor	normal uterine tissue
55	DNA181162 (TAT129)	prostate tumor	normal prostate tissue
	DNA188221 (TAT111)	colon tumor	normal colon tissue
	DNA188221 (TAT111)	liver tumor	normal liver tissue
	DNA188221 (TAT111)	lung tumor	normal lung tissue
	DNA233876 (TAT140)	colon tumor	normal colon tissue

	<u>Molecule</u>	<u>upregulation of expression in:</u>	<u>as compared to:</u>
	DNA233876 (TAT146)	liver tumor	normal liver tissue
	DNA233876 (TAT146)	lung tumor	normal lung tissue
	DNA193891 (TAT148)	prostate tumor	normal prostate tissue
5	DNA193891 (TAT148)	breast tumor	normal breast tissue
	DNA248170 (TAT187)	breast tumor	normal breast tissue
	DNA248170 (TAT187)	prostate tumor	normal prostate tissue
	DNA194628 (TAT118)	kidney tumor	normal kidney tissue
	DNA246415 (TAT167)	kidney tumor	normal kidney tissue
10	DNA215609 (TAT113)	colon tumor	normal colon tissue
	DNA220432 (TAT128)	prostate tumor	normal prostate tissue
	DNA226094 (TAT164)	breast tumor	normal breast tissue
	DNA226094 (TAT164)	brain tumor	normal brain tissue
	DNA226094 (TAT164)	ovarian tumor	normal ovarian tissue
	DNA226094 (TAT164)	lung tumor	normal lung tissue
15	DNA226165 (TAT122)	breast tumor	normal breast tissue
	DNA226165 (TAT122)	endometrial tumor	normal endometrial tissue
	DNA226165 (TAT122)	lung tumor	normal lung tissue
	DNA226165 (TAT122)	colon tumor	normal colon tissue
	DNA226237 (TAT117)	kidney tumor	normal kidney tissue
20	DNA246450 (TAT168)	kidney tumor	normal kidney tissue
	DNA246450 (TAT168)	brain tumor	normal brain tissue
	DNA226456 (TAT144)	breast tumor	normal breast tissue
	DNA226456 (TAT144)	brain tumor	normal brain tissue
	DNA226456 (TAT144)	endometrial tumor	normal endometrial tissue
25	DNA226456 (TAT144)	kidney tumor	normal kidney tissue
	DNA226456 (TAT144)	lung tumor	normal lung tissue
	DNA237637 (TAT188)	breast tumor	normal breast tissue
	DNA237637 (TAT188)	brain tumor	normal brain tissue
	DNA237637 (TAT188)	endometrial tumor	normal endometrial tissue
30	DNA237637 (TAT188)	kidney tumor	normal kidney tissue
	DNA237637 (TAT188)	lung tumor	normal lung tissue
	DNA226339 (TAT126)	colon tumor	normal colon tissue
	DNA226339 (TAT126)	endometrial tumor	normal endometrial tissue
	DNA226339 (TAT126)	ovarian tumor	normal ovarian tissue
35	DNA226339 (TAT126)	pancreatic tumor	normal pancreatic tissue
	DNA236511 (TAT151)	colon tumor	normal colon tissue
	DNA236511 (TAT151)	endometrial tumor	normal endometrial tissue
	DNA236511 (TAT151)	ovarian tumor	normal ovarian tissue
	DNA236511 (TAT151)	pancreatic tumor	normal pancreatic tissue
40	DNA226771 (TAT115)	colon tumor	normal colon tissue
	DNA227087 (TAT163)	breast tumor	normal breast tissue
	DNA227087 (TAT163)	colon tumor	normal colon tissue
	DNA227087 (TAT163)	endocrine tumor	normal endocrine tissue
	DNA227087 (TAT163)	kidney tumor	normal kidney tissue
45	DNA227087 (TAT163)	liver tumor	normal liver tissue
	DNA227087 (TAT163)	lung tumor	normal lung tissue
	DNA227087 (TAT163)	pancreatic tumor	normal pancreatic tissue
	DNA227087 (TAT163)	uterine tumor	normal uterine tissue
	DNA227087 (TAT163)	prostate tumor	normal prostate tissue
50	DNA227087 (TAT163)	bladder tumor	normal bladder tissue
	DNA266307 (TAT227)	breast tumor	normal breast tissue
	DNA266307 (TAT227)	colon tumor	normal colon tissue
	DNA266307 (TAT227)	endocrine tumor	normal endocrine tissue
	DNA266307 (TAT227)	kidney tumor	normal kidney tissue
55	DNA266307 (TAT227)	liver tumor	normal liver tissue

	<u>Molecule</u>	<u>upregulation of expression in:</u>	<u>as compared to:</u>
	DNA266307 (TAT227)	lung tumor	normal lung tissue
	DNA266307 (TAT227)	pancreatic tumor	normal pancreatic tissue
	DNA266307 (TAT227)	uterine tumor	normal uterine tissue
5	DNA266307 (TAT227)	prostate tumor	normal prostate tissue
	DNA266311 (TAT228)	bladder tumor	normal bladder tissue
	DNA266311 (TAT228)	breast tumor	normal breast tissue
	DNA266311 (TAT228)	colon tumor	normal colon tissue
	DNA266311 (TAT228)	endocrine tumor	normal endocrine tissue
10	DNA266311 (TAT228)	kidney tumor	normal kidney tissue
	DNA266311 (TAT228)	liver tumor	normal liver tissue
	DNA266311 (TAT228)	lung tumor	normal lung tissue
	DNA266311 (TAT228)	pancreatic tumor	normal pancreatic tissue
	DNA266311 (TAT228)	uterine tumor	normal uterine tissue
15	DNA266311 (TAT228)	prostate tumor	normal prostate tissue
	DNA266311 (TAT228)	bladder tumor	normal bladder tissue
	DNA266312 (TAT229)	breast tumor	normal breast tissue
	DNA266312 (TAT229)	colon tumor	normal colon tissue
	DNA266312 (TAT229)	endocrine tumor	normal endocrine tissue
20	DNA266312 (TAT229)	kidney tumor	normal kidney tissue
	DNA266312 (TAT229)	liver tumor	normal liver tissue
	DNA266312 (TAT229)	lung tumor	normal lung tissue
	DNA266312 (TAT229)	pancreatic tumor	normal pancreatic tissue
	DNA266312 (TAT229)	uterine tumor	normal uterine tissue
25	DNA266312 (TAT229)	prostate tumor	normal prostate tissue
	DNA266312 (TAT229)	bladder tumor	normal bladder tissue
	DNA266313 (TAT230)	breast tumor	normal breast tissue
	DNA266313 (TAT230)	colon tumor	normal colon tissue
	DNA266313 (TAT230)	endocrine tumor	normal endocrine tissue
30	DNA266313 (TAT230)	kidney tumor	normal kidney tissue
	DNA266313 (TAT230)	liver tumor	normal liver tissue
	DNA266313 (TAT230)	lung tumor	normal lung tissue
	DNA266313 (TAT230)	pancreatic tumor	normal pancreatic tissue
	DNA266313 (TAT230)	uterine tumor	normal uterine tissue
35	DNA266313 (TAT230)	prostate tumor	normal prostate tissue
	DNA266313 (TAT230)	bladder tumor	normal bladder tissue
	DNA227224 (TAT121)	breast tumor	normal breast tissue
	DNA227224 (TAT121)	endometrial tumor	normal endometrial tissue
40	DNA227224 (TAT121)	lung tumor	normal lung tissue
	DNA247486 (TAT183)	skin tumor	normal skin tissue
	DNA247486 (TAT183)	breast tumor	normal breast tissue
	DNA247486 (TAT183)	endometrial tumor	normal endometrial tissue
	DNA247486 (TAT183)	lung tumor	normal lung tissue
	DNA247486 (TAT183)	skin tumor	normal skin tissue
45	DNA227578 (TAT165)	brain tumor	normal brain tissue
	DNA227800 (TAT131)	prostate tumor	normal prostate tissue
	DNA227800 (TAT131)	kidney tumor	normal kidney tissue
	DNA227904 (TAT140)	breast tumor	normal breast tissue
	DNA228199 (TAT127)	uterine tumor	normal uterine tissue
50	DNA228199 (TAT127)	fallopian tube tumor	normal fallopian tube tissue
	DNA228199 (TAT127)	ovarian tumor	normal ovarian tissue
	DNA228199 (TAT127)	lung tumor	normal lung tissue
	DNA228201 (TAT116)	colon tumor	normal colon tissue
	DNA247488 (TAT189)	colon tumor	normal colon tissue
55	DNA236538 (TAT190)	colon tumor	normal colon tissue
	DNA247489 (TAT191)	colon tumor	normal colon tissue

	Molecule	upregulation of expression in:	as compared to:
	DNA231312 (TAT143)	colon tumor	normal colon tissue
	DNA231542 (TAT100)	brain tumor	normal brain tissue
	DNA231542 (TAT100)	glioma	normal glial tissue
5	DNA231542-1 (TAT284)	brain tumor	normal brain tissue
	DNA231542-1 (TAT284)	glioma	normal glial tissue
	DNA231542-2 (TAT285)	brain tumor	normal brain tissue
	DNA231542-2 (TAT285)	glioma	normal glial tissue
	DNA297393 (TAT285-1)	brain tumor	normal brain tissue
	DNA297393 (TAT285-1)	glioma	normal glial tissue
10	DNA232754 (TAT125)	lung tumor	normal lung tissue
	DNA236246 (TAT153)	breast tumor	normal breast tissue
	DNA236343 (TAT104)	breast tumor	normal breast tissue
	DNA236493 (TAT141)	breast tumor	normal breast tissue
	DNA236493 (TAT141)	glioblastoma tumor	normal glial tissue
15	DNA236534 (TAT102)	breast tumor	normal breast tissue
	DNA236534 (TAT102)	lung tumor	normal lung tissue
	DNA236534 (TAT102)	pancreatic tumor	normal pancreatic tissue
	DNA236534 (TAT102)	prostate tumor	normal prostate tissue
	DNA236534 (TAT102)	bladder tumor	normal bladder tissue
20	DNA247480 (TAT142)	lung tumor	normal lung tissue
	DNA264454 (TAT106)	breast tumor	normal breast tissue
	DNA264454 (TAT106)	prostate tumor	normal prostate tissue
	DNA264454 (TAT106)	ovarian tumor	normal ovarian tissue

25 EXAMPLE 7: Use of TAT as a hybridization probe

The following method describes use of a nucleotide sequence encoding TAT as a hybridization probe for, i.e., diagnosis of the presence of a tumor in a mammal.

30 DNA comprising the coding sequence of full-length or mature TAT as disclosed herein can also be employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of TAT) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled TAT-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed 35 in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence TAT can then be identified using standard techniques known in the art.

EXAMPLE 8: Expression of TAT in *E. coli*

40 This example illustrates preparation of an unglycosylated form of TAT by recombinant expression in *E. coli*.

The DNA sequence encoding TAT is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is 45 pBR322 (derived from *E. coli*; see Bolivar et al., *Gene*, 2:95 (1977)) which contains genes for ampicillin and

tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a *trp* promoter, a polyhis leader (including the first six *STH* codons, polyhis sequence, and enterokinase cleavage site), the TAT coding region, lambda transcriptional terminator, and an *argU* gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized TAT protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

TAT may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding TAT is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 *fuA(tonA) lon galE rpoHis(hipRts) clpP(jacQ)*). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g $(\text{NH}_4)_2\text{SO}_4$, 0.71 g sodium citrate \cdot 2H $_2$ O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield lyase SP in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO_4) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfidolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qigen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Urolog grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the

desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded TAT polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 9: Expression of TAT in mammalian cells

This example illustrates preparation of a potentially glycosylated form of TAT by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the TAT DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the TAT DNA using ligation methods such as described in Sambrook et al., *supra*. The resulting vector is called pRK5-TAT.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-TAT DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmapaya et al., *Cell*, 21:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM Na₂CO₃, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The

293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 $\mu\text{Ci/ml}$ ^{35}S -cysteine and 200 $\mu\text{Ci/ml}$ ^{35}S -methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of TAT polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, TAT may be introduced into 293 cells transiently using the dextran sulfate method described by Sunparyrac et al., *Proc. Natl. Acad. Sci.*, 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μg pRK5-TAT DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 $\mu\text{g/ml}$ bovine insulin and 0.1 $\mu\text{g/ml}$ bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed TAT can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, TAT can be expressed in CHO cells. The pRK5-TAT can be transfected into CHO cells using known reagents such as CaPO_4 or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ^{35}S -methionine. After determining the presence of TAT polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed TAT can then be concentrated and purified by any selected method.

Epitope-tagged TAT may also be expressed in host CHO cells. The TAT may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged TAT insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged TAT can then be concentrated and purified by any selected method, such as by Ni^{2+} -chelate affinity chromatography.

TAT may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of two respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Anisbel et al., *Current Protocols of Molecular Biology*, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shifting of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., *Nucl. Acids Res.* 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Qiagen), Duper® or Fugene® (Boehringer Mannheim). The cells are grown as described in Lucas et al., *supra*. Approximately 3×10^6 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μ m filtered PS20 with 5% 0.2 μ m disfiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3×10^6 cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2×10^6 cells/mL. On day 0, the cell number pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 mL Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 mL/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 mL G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 mL Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting

1 ml fractions into tubes containing 275 μ L of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 10: Expression of TAT in Yeast

The following method describes recombinant expression of TAT in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of TAT from the ADHI2/GAPDH promoter. DNA encoding TAT and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of TAT. For secretion, DNA encoding TAT can be cloned into the selected plasmid, together with DNA encoding the ADHI2/GAPDH promoter, a native TAT signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of TAT.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant TAT can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing TAT may further be purified using selected column chromatography resins.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 11: Expression of TAT in Baculovirus-Infected Insect Cells

The following method describes recombinant expression of TAT in Baculovirus-infected insect cells.

The sequence coding for TAT is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding TAT or the desired portion of the coding sequence of TAT such as the sequence encoding an extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BactroGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilly

et al., *Baculovirus expression vectors: A Laboratory Manual*, Oxford: Oxford University Press (1994).

Expressed poly-his tagged TAT can then be purified, for example, by Ni^{2+} -chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., *Nature*, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl_2 ; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.3) and filtered through a 0.45 μm filter. A Ni^{2+} -NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A_{280} with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A_{280} baseline again, the column is developed with a 0 to 500 mM imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni^{2+} -NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₆-tagged TAT are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fe tagged) TAT can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 12: Preparation of Antibodies that Bind TAT

This example illustrates preparation of monoclonal antibodies which can specifically bind TAT.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified TAT, fusion proteins containing TAT, and cells expressing recombinant TAT on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the TAT immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-TAT antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of TAT. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells

which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against TAT. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against TAT is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-TAT monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

Antibodies directed against certain of the TAT polypeptides disclosed herein have been successfully produced using this technique(s). More specifically, functional monoclonal antibodies that are capable of recognizing and binding to TAT protein (as measured by standard ELISA, FACS sorting analysis and/or immunohistochemistry analysis) have been successfully generated against the following TAT proteins as disclosed herein: TAT110 (DNA95930), TAT210 (DNA95930-1), TAT113 (DNA215609), TAT126 (DNA226539), TAT151 (DNA236511), TAT111 (DNA188221), TAT146 (DNA233876), TAT112 (DNA96930), TAT145 (DNA98565), TAT152 (DNA246435), TAT141 (DNA236493), TAT114 (DNA108809), TAT104 (DNA236343), TAT100 (DNA231542), TAT284 (DNA231542-1), TAT285 (DNA231542-2), TAT285-1 (DNA297393), TAT144 (DNA226456), TAT188 (DNA237637), TAT123 (DNA210499), TAT211 (DNA219894), TAT102 (DNA236534), TAT127 (DNA228199) and TAT128 (DNA220432). Interestingly, Applicants have identified that the monoclonal antibodies prepared against TAT111 (DNA188221) and TAT146 (DNA233876) are capable of blocking activation of the EphB2R receptor encoded by the DNA188221 and DNA233876 molecules by its associated ligand polypeptide. As such, antibodies and methods for using those antibodies for blocking activation of the EphB2R receptor (i.e., TAT111 and TAT146 polypeptides) by its associated ligand are encompassed within the presently described invention. Moreover, Applicants have identified that monoclonal antibodies directed against the TAT110 (DNA95930) and TAT210 (DNA95930-1) polypeptides (i.e., IL-20 receptor alpha polypeptides) are capable of inhibiting activation of the IL20 receptor alpha by IL-19 protein. As such, antibodies and methods for using those antibodies for inhibiting activation of the IL-20 receptor alpha (i.e., TAT110 and TAT210 polypeptides) by IL-19 are encompassed within the presently described invention.

In addition to the successful preparation of monoclonal antibodies directed against the TAT polypeptides as described herein, many of those monoclonal antibodies have been successfully conjugated to a cell toxin for use in directing the cellular toxin to a cell (or tissue) that expresses a TAT polypeptide of interest (both *in vitro* and *in vivo*). For example, toxin (e.g., DM1) derivitized monoclonal antibodies have been successfully generated to the following TAT polypeptides as described herein: TAT110 (DNA95930), TAT210 (DNA95930-1), TAT112 (DNA96930), TAT113 (DNA215609), TAT111 (DNA188221) and TAT146 (DNA233876).

EXAMPLE 13: Purification of TAT Polypeptides Using Specific Antibodies

Native or recombinant TAT polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-TAT polypeptide, mature TAT polypeptide, or pre-TAT polypeptide is purified by immunoaffinity chromatography using antibodies specific for the TAT polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-TAT polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CNBr-activated SEPHAROSE[®] (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of TAT polypeptide by preparing a fraction from cells containing TAT polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble TAT polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble TAT polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of TAT polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/TAT polypeptide binding (e.g., a low pH buffer such as approximately pH 2.5, or a high concentration of a chaotrope such as urea or thiocyanate ion), and TAT polypeptide is collected.

EXAMPLE 14: In Vitro Tumor Cell Killing Assay

Mammalian cells expressing the TAT polypeptide of interest may be obtained using standard expression vector and cloning techniques. Alternatively, many tumor cell lines expressing TAT polypeptides of interest are publicly available, for example, through the ATCC and can be routinely identified using standard ELISA or FACS analysis. Anti-TAT polypeptide monoclonal antibodies (and toxin conjugated derivatives thereof) may then be employed in assays to determine the ability of the antibody to kill TAT polypeptide expressing cells *in vitro*.

For example, cells expressing the TAT polypeptide of interest are obtained as described above and plated into 96 well dishes. In one analysis, the antibody/toxin conjugate (or naked antibody) is included throughout the cell incubation for a period of 4 days. In a second independent analysis, the cells are incubated for 1 hour with the antibody/toxin conjugate (or naked antibody) and then washed and incubated in the absence of antibody/toxin conjugate for a period of 4 days. Cell viability is then measured using the CellTiter-Glo Luminescent Cell Viability Assay from Promega (Cat# G7571). Untreated cells serve as a negative control.

In one specific analysis, the ability of monoclonal antibodies directed against TAT112 (DNA96930) were analyzed for the ability to kill cells expressing that polypeptide. In one analysis, an expression vector called gD.NCA was prepared. The TAT112 polypeptide encoding sequences inserted into that vector are driven by an SV40 promoter and the vector also contains the SV40 early poly A signal. The gD.NCA vector was co-transfected into PC3 cells along with an SV40 vector that expresses Neo resistance in PC3 cells, and positive transformants were selected in 800 µg/ml G418. Positive clones were isolated in 96 well plates and analyzed by flow cytometry using an anti-TAT112 monoclonal antibody prepared as described above and called 3B6. Clone 3 was selected for the analysis as it was found to express a high level of TAT112 polypeptide on its surface. In a second independent analysis, the pancreatic cancer cell line, Hpafl II, was obtained from the ATCC and employed in the assay.

The results from the above described assay demonstrated that DM1-conjugated anti-TAT112 monoclonal antibodies were highly efficacious in killing both the TAT112 expressing PC3 cell line as well as the pancreatic cancer cell line Hpafl II as compared to the untreated negative controls.

EXAMPLE 15: *In Vivo* Tumor Cell Killing Assay

To test the efficacy of unconjugated anti-TAT112 monoclonal antibodies, anti-TAT112 antibody was injected intraperitoneally into nude mice 24 hours prior to receiving PC3.gD.NCA clone 3 cells (obtained as described in Example 14 above) subcutaneously in the flank. Antibody injections continued twice per week for the remainder of the study. Tumor volume was measured twice per week.

To test the efficacy of DM1-conjugated anti-TAT112 antibody, PC3.gD.NCA clone 3 cells (obtained as described in Example 14 above) were inoculated into the flank of nude mice. When the tumors reached a mean volume of approximately 100mm³, mice were treated with DM1-conjugated anti-TAT112 antibody intravenously either once or twice per week.

The results of the above analyses demonstrated that both the unconjugated anti-TAT112 as well as the DM1-conjugated anti-TAT112 antibody were highly efficacious in reducing tumor volume in this *in vivo* model. These analyses demonstrate that anti-TAT polypeptide monoclonal antibodies are efficacious for killing tumor cells that express a TAT polypeptide of interest.

EXAMPLE 16: Northern Blot Analysis

Northern blot analysis was performed essentially as described by Sambrook et al., *supra*. Northern blot analysis using probes derived from DNA231542, DNA231542-1, DNA231542-2 and DNA297399 evidences significant upregulation of expression in human glioma tissue as compared to normal human brain tissue.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any

aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to a polypeptide having at least 80% amino acid sequence identity to:
 - (a) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);
 - (b) the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;
 - (c) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide;
 - (d) an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide;
 - (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or
 - (f) a polypeptide encoded by the full-length coding region of the nucleotide sequences shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).
2. An isolated antibody that binds to a polypeptide having:
 - (a) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154);
 - (b) the amino acid sequence shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;
 - (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), with its associated signal peptide sequence;
 - (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 79 to 154 (SEQ ID NOS:79-154), lacking its associated signal peptide sequence;
 - (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78); or
 - (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1 to 78A-B (SEQ ID NOS:1-78).
3. The antibody of Claim 1 which is a monoclonal antibody.
4. The antibody of Claim 1 which is an antibody fragment.
5. The antibody of Claim 1 which is a chimeric or a humanized antibody.
6. The antibody of Claim 1 which is conjugated to a growth inhibitory agent.
7. The antibody of Claim 1 which is conjugated to a cytotoxic agent.

8. The antibody of Claim 7, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
9. The antibody of Claim 7, wherein the cytotoxic agent is a toxin.
- 5 10. The antibody of Claim 9, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
11. The antibody of Claim 9, wherein the toxin is a maytansinoid.
- 10 12. The antibody of Claim 1 which is produced in bacteria.
13. The antibody of Claim 1 which is produced in CHO cells.
14. The antibody of Claim 1 which induces death of a cell to which it binds.
- 15 15. The antibody of Claim 1 which is detectably labeled.

1/162

FIGURE 1

CCAGGATTCGGCAGGAGGTTGACCCGGACAGCTGTCTCTGTGACACCAACCCCGGCTGCTCTTTGTTGGA
TGAGAGCTGCGCTACCTCTTCTGTATTTCTGCTGCAAGGCTTGCTGGCTCAGGCGCAGTATGACCTGGACCCG
CTGCGCGCGTTCCTTGACTACGTCAGTACACCCACTATAGCGACAGATCGACAACCCAGACTACTATGATTA
TCAGAGGTGACTCTCTGCGCCCTCCGAGGAACAGTTCCAGTTCAGTCCAGCAGCAAGTCCACAGGAGTCA
TCCCAGCCCCAACCCAGAACCCAGGAATGCAGAGCTGGAGCCCAACAGAGCTGGGCGCTCTTGACTGCGGTGAG
GAACAGTACCCGTGCACCGCGCTCTACTCCATACACAGGCCCTTGCAAAACAGTGTCTCAACGAGGTCTGCTCTTA
CAGCCTCCGCGGTGTGTACGTCAATTAAACAGGAGATGTGTGTTCGTACAGTGGTGCCACAGGAGGCTCTCTCC
GAGCTGACCTGTGTGCGGACAAAGTCTCCAAATGTGCGGTGATGCGCCAGCAGCGCGCTGTGCGCAATCCGTGGCG
GCTCTCTGTGCCAGGAGCTGTGAGGAGCTGCTAGGAGTGTGCTGCGCATCTCGAGTCTGCGCCCTCTCGGATCTG
GGGCGCTCGGGCCCTGCTGACCTGCTGCTTTTTTTCCCATCCCATGTTCTCTTTTATTCGTAAANAGTTAGT
GGACTGCAGCCTCGGGGTTGCAGGCTGCGGTGCTCAGGCCCCCTCCTTCAGGCTGTGGCCACCTCTGGGGCAC
GATGGGGGCTCCCCACTGCCCCAGTCTGCCCCCTCGGGTTGGGGGAGTATCCAGGCGCTCTCTGTGGGACCTGGGC
CCTTGACGGGCTTCTCAGCGGTTTTTGAGGACAGACAGTCCCCGAGGTAGGCTACATCCCCCACCCAGCT
GCTCTGCTGGATTTCTACAGCCCCGTGGGAGTGGACCACTTTATTTTATACAAATTAATAAACAGTTTTTAC

2/162

FIGURE 2A

CACTAACGCTCTTCTCTAGTCCCGGGCCAACTCGGACAGTTTCTCTATTATTTCGACCGGTCAAGGCTGGCTTG
 TSCCGAACCGCGCGCGCGCGGACGCRGCGACACACACCGGGGGAACTTTTAAANTGAAGGCTAGAGAGAG
 CTCAGCGCGCGCGCGCGCGCGTGGCGGAGGCTCTCGGAGCTGACTCGCCGAGGCGAGGAATTCCTCGGTCGCGA
 GCGCCGCGCGCGCTCGCGCGCGCGCTGGGATGGTGCAGCGCTCGCGCGCGCGCGCGAGCTGCTGCACTGAAG
 GCGGCGGACGAGTGGCGAGCGCGCGCTGGCGGCTGTCCCGCGCGCGCGCTCTCTGCTCGCGCTGGCGGAGCTC
 TGCTCGCGCGCTCGGAGGCGCGGGGTGAGCTTATGGAGCGAAGCGAGAGCTGATGAAGTTGTCAATGCTCTCT
 GTTCGGAATGGGAGCTCTGGATCCGAGTGAAGAGCTTCGACTCCAAGATCATGACGAAGTGTGAAATATTCG
 ACTACACGCGGAAGCGAAGACTGATCAATAATCTGGAAAGAAATGAAGTCTCATTCGCCAGCAGTTTCACGG
 AAACCCACTATCTGCAGAGAGGTACTGATGTCTCCCTCGCTCGAATTACACGGTAATTCCTGGGTCACTGTAC
 TACCATGGACATGTACGGGATATTTCTGATTCAGCAGTCAGTCTCAGACCTGTTCTGGTCTCAGGGGACTTAT
 TGTGTTTGAANAATGAAGCTATGTCTTAGAACCAATGAAAGTGCACACACAGATCAAACTCTTCCAGCGA
 AGAGCTGAANAAGGTCCGGGATCATGTGGATCAGATCACACACACCAAACTCTCGCTGCAAGAAATGTGTTT
 CCACACCTCTCTCAGACATGGCGAAGAGGCATAAAGAGAGAGCCCTCAAGGCAACTAAGTATGTGGAGCTGGT
 GATCTGTGCAGACAAACCGAGATTTCAAGGCGCAGGAAAGATCTGGAAAGATTAAGCAGCGATTAATAGGA
 TTCTGATTCAGCTTGACAGTTTACAGACCACTGAACTCTCGATCTGTGTTGGTAGGCGGTGGAAGTGTGAAT
 GACATGGACAAATGCTCTGATGATCAGGACCCATTCCAGCGCTCCATGAATTTCTGAGCTAGAGGAGAGTGA
 GCTTCTACCTCGCAAAATCCATGACAAATGCGCAGCTTGTGAGTGGGTTTATTTCCAAAGGACCACTCTCGCA
 TGGCCCAATCATGAGCATGTGCACGGCAGACCACTCTGGGGGAATGTCTATGCAACATTGACGAATCTCTCT
 GGTGCGACCTTGACCTTGACATGAGCTGGGCGCAATTTCTGGATGAATCATGACACATCTGACAGGAGCTG
 TAGCTGATCATGGCGTTGAGAAAGGAGCTGATCATGAGACCTTCCACCGGCTACCAATTTCCCTGTTGTT
 TACAGAGTTTGACGAGGAGGACTTGGAGACCGCTCGGAGAAAGGAATGGGGTGTGCTCTGTTTAACTTGCCG
 GAAGTCAGGGAGTCTTTCCGGGGCCGAGATGTGGGAACAGATTTGTGGAAGAGGAGGAGTGTGACTGTGG
 GGAAGCAGAGGAATGATGAATCGCTGCTCAATGCCACCACTGTACCTCTGAAGCGGACGCTGTGTGAGC
 ATGGGCTGTGCTGTGAAGACTGCCAGCTGAAGCCTCGAGGAACAGCGTGCAGGAGCTCCAGCAACTCTGTGAC
 CTCCAGAGTTCGTGCACAGGGGCCAGCCCTCACTGCCAGGCCAACGTGTACCTGACAGATGGGCACTCATGTCA
 GGATGTGGACGGCTACTGCTACAAATGGCATCTGCCAGACTCAGGAGCAGAGTGTGTCAATCTCGGGGACCAG
 GTGCTAAACCTGCCCTGGGATCTGCTTTGAGAGAGTCAATTTCTGCGGTGTCTCTTATGGCACTGTGGCAAA
 GTCTCGAAGAGTTCCTTTGCCAAATGCGAGATGAGAGTGTCTAAATGTGGAAATTCAGATGTGAGGAGGTG
 CAGCGGCGCATGTGATGTACCAATGCGGTTTCATAGAAACAAACATCCCTCTCAGCAGAGGAGGCGGATTC
 TGTGCGGGGGGACCCAGTGTACTTGGGCGATGACATGCGCGAACCGAGGCTTGTGCTTGCAGGCGACAAAGTGT
 GCAGTGGGAAATCTCCCTGAATGTGATGTCAAAATTAATGATGTCTTGGGCTCAGAGTGTGCAATGCA
 GTGCCACAGCAGAGGGGTGTGCAACACAGGAGAACTGCCACTGCGAGGCGCACTGGGCACTCCCTCTCTGTG
 ACAGTTTGGCTTTGGGAGAACACAGACAGCGCGCCCTTCCGCAAGCGATACCAAGGTTTAAACATAGGA
 ATTCCTGGTGAACCTGCTGTCTCTTGTGCTCGGATTTCTGCTTATCTCAAAAGGAAGACCTTGATAGGACT
 GCTGTTTACAAATAGAGAGACCACTTGAAGAACTAAGGTGTGTGCGCCCTTCCCGGCGACCCGCTGGCTTCC
 AACCTGTGACGCTCACTCGCGCACTTGGAAAGGCTGTGAGAGAGCGCGCAGATTCCTACCCACCGAAG
 GACAAATCCAGGATTTGCTGCACTGTCAAAATGTTGACATCGCAGACCCCTCAAGCGGCTGATGTCTCTCA
 GCGCATCTCACTCAGGAGGCTTCTCTCTCCACCGGCGCTACGTGCACTTACGCTTCCCTGCGCAGACCC
 TGCCACCCAGGCTGCACCTTAGCGAGGCCAGGGGACCTGTAGGCCAAACCCCTCAGAGGCTCTGCTGTCA
 GATCTCTGGCGAGAACACTCGGCTCACTGCTGCTTGCAGGACCCACAGACATGGGAGACTGGGCTCGG

3/162

FIGURE 2B

CTTGGCACCCCTCGAGCCTGCTCCACATATCCACACCAAGTSCCCAGATCCACCCACACCGCCTATATTAAGT
GAGGAGCCCGACACCTTTTTTCAACAGTGAAGACAGAGTTTGACACTATCTTTGAGCTCCAGTTGGAGTTTTTIG
 TACCACACTTTTAGGATTTTTTTAATGTTTTAAACATCATTAATAAAGAACTTTGAGCTACTGCCGTGAGTG
 TGTGCTGTGCTATGGTGCTCTGTCTACTTGCACAGGTACTTGTAAATATTAATTTTATCGAGATGTTGATTAC
 AGTGCAGTGGCTGTAGTAGGCATTTTTACCATCACTGAGTTTTCCATGGCAGGAAGGCTTGTTGTCTTTTAG
 TATTTTGGTGAAGTTGAATATCTGCTTGATGGGATTCGGACAGAGTGTGTTGCTTTCTGATCAAGGCCCTT
 ATTGGAAGACAGTGTCCCAACTAOCOCAGCTGTGCTTATGATACAGATGGAGCTCAAGAGATCCCAAGTAGA
 AFTCTAGTGTGATTTTTCGGATTCCTCATCTCGAGCCAGAGCCAAAGGAGCTTCAGGTCCAGGCTGTGTTGG/TT
 TCGAGGAGGCGCTGTGCCCCCTGACAACTGGCAGGCGAGGCTCCAGGGACGCTGGGAGAAATCTGGCTCTGG
 CCAGGAGGCTTTGGTGAGAACCTGGGTTGCAGACGGAACTTTAAGGTGTAGGCCACACCGAGATAGAGACTGGA
 ACATAGACAAAGCCAGAACTTGACCTTGAGCTGACCCAGCGGTGAGCATGTTTGGAGGGGCTGTGATGTCTACT
 CAGGCGGTGCTGTAGAGAAATGCCAGCACTTCTTTTTCTGGCTGTCTTTCTAGAGCACTGCCACCGTAGG
 TTATTTAGCTTGGCAAGGTGGTGTCTGTGTAAGAACCTACTGCCAGGCACTGCAACCCGCCACCTCTCTAT
 ACTGCTTGGAGCTGAGCAAAATCACCACAACTGTAAATACAAATGATCTGTATTGAGACAGATGAGGACTTTCCA
 TGGGACCACAACATATTTTCAGATGTGABCCNTTAACAGATCTAGTCAATCAAGTCTGTTTACGCAAGGTTCA
 ACTTATTACAAATTAGGCAGACTCTTTATGCTTGCAGAAACTACAAACCAATGGAAATGTGATGTTTCATGGGTATA
 GTTCATGTCTGCTATCAATATCTGATAGATATTGGACAAAGAACCTTCTCTAGGGGCTCTCTTTTTCCAACT
 TGGCTGCAGGAATCTTTAAAGATGCTTTTAACAGAGCTCTGAACCTATTTCTTAACCACTTGCACCACTACCTGT
 TGGCATCAGCAATGTGCAAGGAAATCAACTGCTTATCAACTTCCAAATATTTATGAGATGTGGCTTGGGC
 AGCTGCCCTTGAACTCTCACTCTTCAAAATGCTGACTAGGAGGCCATGTTTCAAGAGTCTTTAAAGTGACT
 AATGGCATGAGAAATACAAAAATACTCAGATAGGTAAGATGCCATGATGCTCTGTCTTCTGGACTGGTTTTT
 ACATAGAGACAAATGACAAAGCTTACATAATCACTCTGAGTGTTTTATGAGGAAGCCCTTCTTTTGGGGTCA
 ACAGTTTTTCTATGCTTTGAACAGAAAAATATGTACCAAGAACTCTTGTTTGGCTTCCAGAAACAAACTGCA
 ATTTCACTTTCCCGGTGTTCCCACTGTATCTAGGCAACATAGTATTCATGACTATGGAATCACTCAACAGT
 ACACAAACACACACAAAGGGAACCCAGCTCAATACATTTCCAACCTGATATAGCATGCATCTGTTTATCTATA
 GTTATTATAGTTCTTTAAAAATGTAAAGCCATGCTGGAATTAATACTGCTGAGATACATACAGAAATTAAGTGAAC
 TGTATTACCTTTGGTAAATGTACTAAAGCCAACTATATATATATATTAATAAAGGTTTACAGAAATTTATGGTGC
 AATTACGTGGGCATTGTCTTTTAGATGCCAACTCCCTAGATCTGGCATGTTAGCCCTTCTCCCAATTAAGA
 GGAATAGAACAAAAAATAAAAAA

4/162

FIGURE 3

GGAGTTCCTCAAAGAGGCCGAGTAGGTCTCTGAGATCCTTCGCACAGCTACATCCTCAGGGTGGAGGAAAGATG
GCTTCCAGAGAGCTGCGCGCTGCTCTCTTCTGCTGAGCTGCCGCGCCAAACAGAGAGAGTCTCTGGGTGATATCATCAT
GAGNCCCGAGCTGTGCTCTGGATGGCTTTTACCAACAAGTCAGATGCTATGGTTACTCTCGGAGAGCTGAGAGACT
GCTCTGAGGCGGAGCTCGAGTGTGAGTCTTACGGAGAAAGCCAGGACCACTGGATCTATCTACCTGAGTTTAAAGGAA
GCCAGCACCATAGCAGAGTACATAGTGGCTATCAGAGAGGCCGCGCATTTGGATTGGCTGCACGACCCACAG
GAAGAGAGAGCTGGCTGGCAGTGGATTGATGGGGCCGTTATCTGTACAGAGATCTGCTTGGCAAGTCTCTGGTGTG
GGAGACCAAGCACTGTGCTGAGATTAGCTCCATTAACAACCTTTTAACTTGGCGAGGACCGATGCCACAGCCGC
CACACTCTCTGTGCAAGTACCGAGCCATGAGTGAAGAGAAATCAGAGTTCTGCTACTCTGCGACAGCCCGCTCTC
TTCTCTTCTGCTAGCTGGCTAAATCTGCTCATTTATTTACAGAGGGGAAACCTAGCAAACTAAGAGTGATAGGG
CCCTTACACCACTGGCTTTTATGGCTTAGAGACAGAGAACTTAGACATTGGCCCGAGTAGGGCTCTAGAGCTTAA
ATGTTTGGCCCGCATCTCCCTTCCACAGATATCCTCTTCCCTCCCTCCCTGTCTTGGCTCTCTCGACAGCTGT
AGAAATAGTGATCTCCAGCGCTATGAAGACAGCTGGGCTTTTGGCCATAAGAAATGAAGATTGAAGACAGAGAGGA
AGAAATCTAGGAGTAGCTTCTAGACCCCTTCAGCTTCTACACCTTCTGCGCTCTCTGCTTTGCTGACCCCC
ACCCAGGCCATCTCATCTCTGCTGTTTTCTCTTGGGCATAGGAGGTTTACAGTAGAGATCCTTGTCTAGGTT
GATGTGGGCTAAATTTCCTTTATATAAACCATTTGTGTACATAAAAAAATAAAAAAATAAAAAAATAAAAAA
AAAAAATAAAAAAATAAAAAAATAAAAAAATAAAAAAATAAAAAAATAAAAAAATAAAAAAATAAAAAAATAAAAAA

5/162

FIGURE 4

GGGGAGCAGAGAGGAGGCAATGTCACCATTCGAGAACAGGTGATCTGGCCCTGGTCCTGGTGTCCATGCTGG
CCCTCGGCACCTCTGGCGGAGGCCAGACAGAGACGTGTACAGTGGCCCCCCTGAAAGACAGABTTCTGGTTTT
CCTGGTGTACGCCCCCTCCAGTGTGCARRTAGGGCTGCTGTTTGCACGACCCGTTCTGTGGGGTCCCCGGTG
CTTCTATCCCTAATCCATCGAGCTCCCTCCAGAGAGGAGTGTGAATTTAGACACTTCTGCGGGATCTGCT
GCATCCTGACGCGGTGCCATCCCCAGCACGGTGAATTAATCCAGAGCTCGGCTGCCACCTCCACCGGACCTC
AGACACGCTTCTGACGCTGTGCTCGGCTCACACACAGATTGACTGCTCTGACTTTGACTACTCAAAATTCGC
CTAAAATTAAGAGCTCGATATTAATA

7/162

FIGURE 6

CATTGCGGCTGCCGCGGTGCTGCTGTTGCTCTGGGGGCCCTTGGGGACGGGCACTTCCTGTGTCTCTGCTG
 GTTTCCTAAACCTGCACACATCACTTCTTATCCATCAACATGAGAGATGTCTACAAATGGACTCCACCCAGAG
 GGTCTTCAGGAGTTAAAGTTACTTACACTGTGCAGTATTTCAATATATGGCCAAAGAAATGGCTGAATAAATC
 AGAATGCAGAAATATCAATAGAACCTACTGTGATCTTTCTGCTGAACCTCTGACTACGACACCCAGTATTATG
 CCNAGTTAAGGCCATTTGGGGACAAAGPGTTCABATGGGCTGAAAGTGGACGGTTCTATCCTTTTTAGAA
 ACACAAATTTGGCCACCGAGAGSTGGCACTGACTACAGATGAGAAGTCCATTTCTGTGTCGTGACAGCTCCAGA
 GAAGTGGAGAGAGAAATCCAGAGACCTTCCTGTTTCCATGCAACAAATATCTCCATCTGAAATATAAGCTCT
 CTGTGTTGATACTAAATCAAAACAGAACGTGGTCCCACTGTGTGACCAACCCACGCTGGTGTCACTGGCTG
 GAGCCGAACACTCTTTACTGCGTACACGTGGAGTCTTCTGTCCTAGGGCCCTCTGCGCGTCTCAGCCTTCTGA
 GAAGCAGTGTGCCAGGACTTTGAAGATCAATCATCAGAGTTCAAGGCTAAATCATCTCTCTGTATGTTTGC
 CCATATCTATTACCGTGTTCCTTTTCTGTGATGGGCTATTCCATCTACCGATATATCCAGTTGGCAAGAG
 AAACACCCAGCAAAATTTGATTTTGATTTATGGAAATGAATTTGACAAAGATTCTTTGTGCTGCTGAAAAT
 CGTGATTAACCTTATCACCTTCATATCTCGGATGATTTCTAAATTTCTCATCAGGATATGATTTACTGGGA
 AAGCGATGATGATATCCAGCCTTAATGATCTCAGCCACGCGGAACTGAGGCCCTCAGGAGGAAGAGAG
 GTGAACATTTAGGGTATGCTTCGCAFTTGATGGAAATTTTTGTGACTCTGAAGAAAACACCGAAGGTACTTC
 TCTCACCAGCAAGAGTCCCTCAGCAGAACATACCCCGGATAAAACAGTCAATGAATATGAATATGATGTCA
 GAACCACTGACATTTGTGCGGGGCTGAAGAGCAGGAGCTCAGTTGCAGGAGGAGGTGCTCCACACAGGAACA
 TTATTTGAGCTCGCAGGACAGCTTGGCAGTCTTTGGGCCCGCAACGTTACAGTACTCATACACCCCTCAGCTCCA
 AGACTTAGACCCCTGGCGCAGGAGCACACAGACTCGGAGCGAGGGCGGAGGAGAGGCCATCGACGACCTGG
 TCGACTGGGATCCCAACATGGCAGCTGTGTATCTCTCGCTGCCAGCTTCGACCAAGGATTCAGAGGGCTGC
 GAGCCTTCTGAGGGGATGGGCTCGGAGAGGAGGCTCTTCTATCTAGACTCTATGAGGAGCCGCTCCGACAG
 GCGCCAGGAGAAATGAACCTATCTCATGCAATTCATGGAGGATGGGGTTATATGTGCAGATGGAATCT
 GATGCCACACTCTCTTTTGCCTTTGTTCTCTGTGCAACAGATGATCAGCCCTTTGATCCCGACGATAAG
 TACCTGGGATGAAGAAAGTTTTTTCAGTTTGTCAGTGTCTGTGAGAA

FIGURE 7

AGCGGGCGCTGGGACTGAGCAGTCTGCTGCCCCCGACATGTGACCCAGCCCCGCCGCCCAAGCGGGCTCCCGGC
 CGCCCGGCCCTGCGGCCGAGCTGCCCKTSCCGCGCGCTGCTGCTGTTGCTTCCCTGGCGGCGCCTTGGGGACGGGGAGT
 TCCCTGTGTCTCTGGTGGTTTGCCCTAAACCTGCAAAACATCACTTCTTATCCATCAACATGAAGAAATGTCTTAC
 AATGGACTCCACCAGAGGGTCTTCAAGGAGTTAAAGTTACTTACACTGTGCAGTATTTCATATATGGGCNAAAG
 AAATGGCTCAATAAATCAGAAATGCAGAAATATCANTAGAACCTACTGTGATCTTCTGCTGAAACTTCTGACTA
 CGAACACCGAGTATTATGCAAAAGTTAAGGCCATTTGGGGAAACAAAGTGTTCCAAATGGGCTGAAGATCGACGGT
 TCTATCTTTTTTGGAAACACAAATTTGGUCCACCGAGAGGGGCACTGACTACAGATGAGAAGTCCATTTCTGTT
 GTCTTGACAGCTCCAGAGAAAGTGGAAAGAAATCCAGAAAGACCTTCCCTGTTTCCATGCAACAAATATACTCCAA
 TCTGAAGTATAACCTGTCTGTGTTGAAATCTAAATCAAACAGAACCTGGTCCCAGTGTGTGAACCAACACACCGC
 TGGTGTCTACCTGGCTGGAGCCGAAACCTCTTTACTGGCGTACACGTGGAGTCCCTCGTCCCAGGGCCCCCTCGC
 CGTGTCTCAGCCTTCTGAGAAAGCAGTGTGCCAGGACTTTGAAAGATCAATCATCAGAGTTCBAGGCTAAAAATCAT
 CTCTGGGTATGTTTTGCCCATATCTATTACCGTGTTCITTTTTCTGTGATGGGGCTATTCATCTACCGATATA
 TCCACGTTGGCAAAGAGAAACACCCAGCAAMTTTGATTTTGATTTATGCAATGAATTTGACAAAGATTCTTT
 GTGCTCGCTGAAAAAATCGTGATTAACCTTTATCACCTCAATATCGCGGATGATTTCTAAATTTCTCATCAGGA
 TATGAGTTTACTGGGAAAAGCAGTGATGTATCCAGCCTTAATGATCTTCAGCCACAGCGGGAACCTGAGGCCCC
 CTCGGGAGGAGAGAGGAGGTGAAACATTTAGGTTATGCTTCGCATTTGATGGAAATTTTTTGTGACTCTGAAGAA
 AACACGGAAGGTACTTCTCTACCCAGCAGAGTCCCTCAGCAGAAACAATACCCCCGGATAAACAGTCAATTGA
 ATATGAATATGATGTCAGAACCACTGACATTTGTGCGGGGCCCTGAAGAGCAGGAGCTCAGTTTGCAGGAGGAGG
 TGTCCACACAGGAACATTTATGGAGTCGACAGCGAGGTTGGCAGTCTTGGGXCXCGCAACGTTACAGTACTCA
 TACACCCCTCAGCTCCAAAGACTTTAGACCCCTGGCGCAGGAGCACACAGACTCGGAGGAGGGGCGCGAGGAAGA
 GGCATCGACAGCCCTGGTCGACTGGGATCCCAAACTGGCAGGCTGTGTATCTTCTGCTGTCCAGCTTCGACC
 AGGATTCAAGAGGCTGCGAACCCTTCTGAGGGGATGGGCTCGGAGGAGGGGCTTCTCATCTAGACTCTATGAG
 GAGCGGCTCCAGACAGGCGCACGAGGAAATGAAACCTATCTCATGCAATTCATGGAGAAATGGGGTTATA
 TGTGCAGATGGAAAACTGAATGCCAACACTTCTTTTGGCTTTTGTTCCTGTGCAACAGGTGAGTCAACCCCTT
 TGTATCCAGCCATAAGTATACCTGGGATGAAGCAAGTTTTTTCCAGTTTCTAGTGTCTGTGAGAA

10/162

FIGURE 9

GAAGGACAGCAGGGGCCACAGTCACAGTAGCCCTGACCNAGCATTCTTGGAGCTCAGCTCCTCTACAAAGAG
 GTGGACAGAGGAAGACAGCAGAGACCATGGGGACCCCTCAGCCCTCCCTGCGAGATTGCATGTCCCTGGAAGG
 AGGTCTGTCTCAGAGCCTCACCTTCTAACTTCTGTGAACCCACCACCCTGCCCAGGTCTACTATTGAATCCAG
 CCGTTCAATGTGCGAGAGGGGGAAGGAGGTTCCTCTACTCCGCCCAACCTGCCCGAAGATCGTATTTGGTTACAG
 CTGGTACAAAGGCGAAGAGGTGGATGGCAACAGTCTAATTGTAGGATATGTATATAGGAAGCTCAGCAAGCTACCC
 CAGGGCCCCGATACAGTGGTCGAGAGACAAATATACCCCAATGCATCCCTGCTGATCCAGAAAGTCAACCAAGAT
 GACACAGGATTCATATACCTACAGTCTATAAGTCAGATCTTGTGAATGGAAGACACCCGACAGTTCCATGT
 ATATCCCGGAGCTGCCAAGGCCCTCCATCTCCAGCAGCAACTCCACCCCGTGGAGGACAAAGATGCTGTGGCCT
 TCACCTGTGACCTGAGGTTTCAGAACACCACTACCTGTGGTGGTAAATGGTCAGAGCCTCCCGGTGAGTCCC
 AGGCTGCAGCTGTCCATGGCAACATGACCTCCTACTCAGCGTCAAAAGGAACGATGCAGGATCCTATGA
 ATGTGAATACAGAACCCAGCGAGTGCACACCGCAGTGACCCAGTCACTGATGCTGCTATGGCCGATG
 GCCCCACCAATTTCCCTCAAAAGGCCAATTACCGTCCAGGGGAAAATCTGAACCTCTCCTGCCACGACCTCT
 AAGCCACCCGCAAGACTCTTTGGTTTATCAATGGAGGTTCCAGCAATCCACNCAAGAGCTCTTTATCCCCAA
 CTTCACTGTGAATTAATACGGGATCCCTATATGTGCCAAGCCCTAAGTCACTCAGCCACTGGCCTCAATAGGACACAG
 TCACGATGATCAGCTCTCTGGAGATGCTCTGCTCTCAGCTGTGGCCCGCTGGCAGTACAGATTGGAGTG
 CTGGCCAGGTTGGCTCTGATATAGCAGCCCTGGTGTATTTTCGATATTTTCAGGAAGACTGGCAGATTGGACCG
 ACCCTGAATTTCTGTAGCTCCTCCAAATCCCTTTTATCCCATGGGAACCACTAAAACAAAGGTCTGCTCTGCTCC
 TGAAGCCCTATATGCTGGAGATGGACAACCTCAATGAATTTAAAGGGAAAACCTCAGGCGTGAAGTGTGTGC
 CACTCAGAGACTTCACCTAAGTACAGAGACAGGCAACTGCACCAATGGTGAGCAATTAAGCACTTCAAGTATG
 GACAGCTTTTCCCAAGTGTCAAAACAAAGCTCCTCATCATGATAAGGCTCTTACCCCTTTTAAATTTGCTCCT
 GCTTATGGCCTGCTCTTTTGGCTTGGCAGGATGATGCTGTGATAGTATTTACAGAGAGTATGCTCAGAGGGA
 ACTTAACAGAGTATCAGATCTATCTGTCAATCCCAAGCTTTACATAAATTAAGAGATCTCTTATGACCCCA
 GTGACTACATTAAGCAGCATCTTTACACAGCCCTGTGTTCAATGTACAGTGGTCTCTTTCAGAGTTGGACTT
 CTGACTCTCCTGTTCTCACTCCCTGTTTATTAACACAGCCACTGCATGCCAATATAGAAATGCTCCCT
 ACCAGCTGAACAGGAGGAGTCTGTGCAGTTTCTGACACTTGTGTGAACCTGGCTAAATACAAATGGGTATCG
 CTGAGACTAAGTTGTAGAAATTAACAAATGTGCTGCTTGGTTAAATGGCTAGACTCTCTCTGACTCATCTTTA
 TTCTATTTTATGTTGATTTGTATCTGCTTGAAGTGGTGTCCAACTCTTGGTATTACCTCTCTTATAGTCATA
 CTAGTACTCATCTCCTCTGGTGTAGTGTATCTCTAAAAGCTTTAAATGTCTGCATGCAGCCAGCCATCAATA
 GTGAATGGTCTCTCTTTGGCTGGAATTACAAAACCTCAGAGAAATGTGCTCTCAGAGAGACATCATAAACCATGA
 AGGATAAAAGCCCCAATAGGTGGTAACTGATATAGCCTAATGCTTTAAGATTGGTCACACTCTCACCTAGG
 TGAAGCATTTAGCGAGTGGTGCATAAATGCTACACTCCAACTGAATGTTAAGGAGAGATGATCCAAAT
 TAAAAAAATTAAGAACCAATTTAAAAAAAGGAACAGGAGATTCAGTCTACTTGAATAGCATATATACA
 GAGTCCCTCTACTTTTAACTTTTACAAAAAAGTAACCTGAACATACTGATGTTAAACCAATGATTTATTTCT
 GTGGTCTGTTCTGTTGCTGCTTGAATTTGAACCAACCTGCTCTGATTTGATTTGCCAGGGGGAGCTATCAC
 TGTACTTGTAGGTGGTGTGCTTAACTTAACTATAAATCACAATAAAAGCAATTAAGCTCTAAAAAAGGGA

FIGURE 10

[illegible]

FIGURE 11

[illegible]

13/162

FIGURE 12

[illegible]

14/162

FIGURE 13

AGCCAGCTCAGGCTACACTATCCAGGATCAGCATGCCCCGTCCGCCAGTGGGTAAATCGCCCTGGCCTTGGCTGC
CCTCCTTGTGTGGACAGGGAAGTGCCAGTGGCAGCAGGAAGCTCCCTTTCTCAGGANTGCCATCTGTGAAC
ACATGGTAGAGTCTCCAACTGTCTCCAGATGTCCAACTGGTCTGGGGACTGATGGGCTCACATATACGAAT
GATGCCAGCTCTGCTTGGCCGGATAAAAACCAACAGGACATCCAGATCATGAAGATGGCAANTGCTGATC
CCACAGGAGCACTCAGGCCATGAAGTGTCAAGTGGAGACAGTGGTGGCATGGAGAGGATATGACATGAAT
AAAGCATCCAGCCAAAAAAGAAAAA

16/162

FIGURE 15

TCCACATCCAGGTCITTTGTGCTCCTCGCTTGCCTGTTCCITTTCCACGCATTTTCCAGGATAACTGTGACTCGA
 GGGCCCGCAATGGATGCCCTGCAACTAGCAAAATCCGGCTTTTGCCGTTGATCTGTTTCAACCACTATGTGAAAAG
 GAGCCATCGGGCAATGTCTCTCTCTCCAACTCTGCTCTCCACCTCTCTGTCACTTGTCTCAAGTGGGTGCTAA
 AGGTGACACTGCAAATGAAATGGACAGGTTCTTCATTTTGAAATGTCAAAGATGTACCTTTTGGATTTCAA
 CAGTAGCATCGGATGTAAACAACTTAGTTCCTTTTACTCACTGAACATAATCAAGCGGCTCAACGTAGACAAA
 TCTCTGAATCTTTCTACAGAGTTCTATCAGCTCTACGAGAGACCGTATGCAAGAGGANTGGAACCTGTGACTT
 CAAGATTAATTTGGAAGAAACGAAGGTCAGATCAACACTCAATTAAGGATCTCAAGATGGCCACTTTGGA
 ACAFTTTAGCTGACAAACAGTCTGAACGACCCAGACCAAAATCCTTGTGGTTAATGCTGCTACTTTTGTGGCAAG
 TGGATGAGAAATTTTCTGAATCAGAAACAAAAGATGTCTTTCAAGTCAACAGACAGACCAACACCACT
 GCAGATGATGAACATGGAGGCCACGTTCTGTATGGGAACATTCAGACTATCAATTTGAAGATCATAGAGCTTC
 CTTTTCAAABTAAGCATCTCAGCATGTTTCATCCTACTACCCAGGATGTGGAGGATGATCCACAGGCTTGGAG
 MAGATTGAABAACTCACTCACTCAGAGTCACTGTCAAGTGGACTAATCCAGACCAATGGCCATGGCAAGGT
 CAACCTCTCCATTCCAABTTTAAGGTGAAAAGATGATTGATCCACAGGCTTGTCTGGAATCTAGGGCTGA
 AACATATCTTCAGTGAGACACATCTGATTTCTCTGGATGTCAAGAGCAAGGGAGTGGCCCTTCAATATGTT
 ATCCCAAAAGTGTCTTAGAATAAATCAGAGTGGTGGGATTCATAGAGGTGCCAGGACAGGATCTCTCA
 GCACAGCATGAATGAATGCTGACCATCCCTTTTTCATCATCAGGCACCAACCACTCGAAACATCATTT
 TCTTGGCAATTTCTGTTCTCTTAAATGGCTAGGCCATGTTAAGTCTCTCCCTGACTTTTCTGTGGATGCCGA
 TTTCTGTAACTTGCATCCAGAGATTCATTTCTAGATACATAAATTTGCTAATGTTGCTGGATCAGGAAGCC
 GCCAGTACTTTGATATGTAGCCCTTCACACAGATAGACCTTTTTTTTTTCCAACTTACTCTTTTGTCTCCTT
 TTTTCCATAGACAAATGACATACGCTTTTAATGAAAAGGAATCACGTTAAGCAAAAATATTTATTCTATTAT
 TGTCAATTTCTCGGCTTAGTTGGCAGAAATACAGTCTTCCCAAAAGAAAATTCCTATAAGGAGATTTGGAAG
 CTCTTCTTCCAGCACTATGCTTTCTTCTTTGGGATAGAGATGTTCCAGACATCTCTGCTTCCCTGAAGAC
 TGAAGAAAGTGTACTGCTAGGGACCCAGAACTGCCCTGGCTCCATGAACCTTGGGCATGCTCAGGCTAC
 TATAGGTCGCAAGTCTCTATGTTAAGCCCTGGCAGGCAAGGTGTTATTAATTTCTGAATTTTGGGATTTT
 AAAAGATAATATTTTACATACCTGTATGTTTATAGAACTTCATGGATCAGATCTGGGGCAGCACCTTATAATC
 AACACCTTATATGCTGCAACAAATGTGAATATTCAGACAAATGGATACATAAGAGCTAAGTAGCCCATAA
 GGGGTCAAATTTGCTGCCAAATGCGATGCCCACTTACAAAACACTTCCGTTCCGACAGCTTTTCAGAT
 GTGGATGTTTGATAAGGAATATAGACCTCTAGTAGCTGAATGCAAGACCCCAAGAGGAGTTTCAATCTTA
 ATATAATTCATTTTCTTTTGTAGATCTGCTCATCTGGCTATTGCTTGGCTAGCTGGTGGCAGGGGCT
 TCTAGCTGACTTGCACAGGATTTCTCAGATAGCCATCAGAAATTTGTGTTGAAGAACTTGTCTCTTCATC
 TATATGATAGCGGAAAGGAGAGGAACCTACTGCTTTAGAAAATATAAGTAAATGATTAAGTGTCTCAGG
 TTACCTTGACACATAGTTTTTCAGTCTATGGGTTAGTTACTTTGATGGCCAGGACGTAACTTATATTAATAG
 TAATTTGAAGGTGGTGGATAAGCTATCCGTTGTCAGGTTTCATGGATTACTTCTCTATAAAAAATGTGTAT
 TTACCAAAATTTTGTGACAAATTTCTCCATCTCTTCCITGACCTGATTTGTAATAGGTTCTCTCTGCTCT
 GAGATTCATATTAATTTTCTCTATGCTATTGACATAAATATTTTGAAGTACA

17/162

FIGURE 16

GCCGAGCGGSGCTCCGGAAGCCGGCCGGGGGGCCGCGGSCCTGCGGGGCGTCAATGATCGCCACTCCAGCTA
 CATCTTCATCTGGCTGCAGCTGGAGCTCTGCGCCATGGCCGTGCTGCTCACCAGGGTGAATTCGATGCTACT
 GTGATGCTGCCCACTGTGTAGCCACTGGTTATATGTGTAAATCTGAGCTCAGCGCCCTGCTTCTCTAGACTTCTT
 GATCCTCAGAACTCAATTCGCCACTCACCCTGGCTGCTGGACTCTCTTGCCAGCAGGACGACGACATCTGCCA
 AGCCAAACAGGCCCCGAAACCACTCTGGCAGCCACATACCCACATTTGCATGCTGTGATGAAGACATGTGCAATT
 ACAGAGGGCTGCACGATGTTCTCTCTCCTCCAGGGGTGAGGCCCTCAGGACAGGAACAGGTATCAGCCTGAT
 GGTAGCAGAAACCTTATCACCAAGGTGCAGGAGCTGACTTCTTCCAAAGAGTTGTGGTTCGGGCGAGCGGTCAF
 TGCCCTGCCCCATTTGCTGGAGGGCTGATTTTAGTGTTCCTTATTATGTTGGCCCTGAGGATGCTTGGAGTGA
 ATAAGAGGCTGCAGGATCAGCGGCAACAGTGTCTCCCGTTTGCCACTACAGCTTTCACGGACACCATTCGAAA
 AAGGGGCAGGTTGCAAGTTAGACTTGGAAATGCATGGTGCCGGTCAGTGGGCGACGAGACTGCTGTCTGACCTG
 TGATAAATGAGACAGCGAGACTCAGCAACGATAGATCCTCTCGCTTGTTCAGTGGGCGATGTACAGTGGGC
 ACGGGAGCTGGAAATCGTATGACGGAGTCTTATCTGAACACACTTACTGAACAGCTTGAAGGCTTTTGAAT
 TCTGCTGGACAGGAGCACTTATCTGAAGACAAACTCATTTAATGATCTTTGACAGCAAAATGACCTCTGCAA
 ACAGCATCTTGGATATTTCTTCTGAAGGATTATTTGCACAGACTTAAATACAGTTAATGTGTTATTTGCTTTT
 ARAATTATAAAGCAAGAGGAGACTTTGTACACACTGTACACAGGTTATTTGCATCCACGGGAGCTGGAAT
 TGAGTACCTAAATACAAAATGTGCCCTAAAA

FIGURE 17A

GTCACCTAGGPAAGGGTGTCCCTTCGGGCGAGCGGGCTCAGCATGAGGAACAGAGGAATGACACTCTGGACAG
 CACCCGGGCCCTGTACTCCAGCGSOUTCTCGAGCAGACTTGTCTTACAGTGAAACCGATTTGGTGAATTTTFA
 TTCAGGCAATTTTARGAARCCGGAATGTGTCTCTTTACCAAAGATTCAGAGCCCAAGGAAATGTGTGCAAG
 TGTGGCTGTGCCAGAGCCAGACATGGAGGACCACAGATCAACCAAGGTGGAATGTGAATACAGAAACA
 CACCAAGGAATTTCTACCGAGCGCTTTGGGATATTCTAGTTTGAACACTGGGAGAGAGAGGAGTATATATAC
 GTCTGTCTCTGACAGACCGAGCGGGAATCCTTTACGAGCTGTGTGACTAGCACTGGCACTGGAAACACCCAAAC
 CTGGTCAATTTCTGTGACCGGGGCGCCAAAGAACTTCGCCCTGAAAGCGGATCGCAAGATCTTCAGCCGGCT
 CATCTACATCGCGCGAGTCCAAAGGTGCTTGGATTCTCACGGGAGGCCACCATTTATGGCCTGACGAAGTACATCG
 GGGAGTGGTGGAGAGATAACACCATCAGCAGGAGTTTCAGAGGGAATATTGTGGCCATTGGCCATAGCAGCTTGG
 GGCAATGGTCTCCAAACCGGACACCTCTATCGAATATGGCGATGCTGAGGGCTATTTTTAGCCCAAGTACCTTAT
 GGATGACTTCAAGGGATCCACTGTATATCTGSAACACACCCACACACATTTGCTGCTCGTGGACAATGGCT
 GTCATGGACATCCCCTGTGGAAGCAAAGCTCCGGAATCAGCTAGAGGAACATATCTCTGAGCGCACTATTCAA
 GATTCGAACATGCTGAGCAAGATCCCATTTGTGTTTTTGGCCAAAGGAGTGCAGAAAGAGACTTTGAAAGCCAT
 CAATACCTCCATCAAAATAAAATTCCTTGTGTGGTGGTGGAGGGCTCGGGCCGGATCCGCTGATGTGATCGCTA
 GCTGTGGTGGAGCTGGAGGATGCCCGACATCTTCTGCGCTCAAGGGAAGCTGGGAGCTTTTACCCCGCAGG
 GTGTCCCGGCTGTCTGAGGAGGAGACTGAGAGTTGGATCAATGGCTCAAGGAATTTCTCGAATGTTCCTCACT
 ATTACAGTTTATTAATGGAGAAGCTGGGGATGAATTTGTAGCAATGCCATCTCTAGCTCTATACAAAG
 CCTTCAGCACCACTGAGCAAGSACAAGGATACTGGAATGGCCAGCTGAAGCTCTGTCTGGAGTGGAAACAGCTG
 GACTTAGCCCAATGATGAGATTTTCAACCAATGACCCGCGATGGAGCTGTGCTGACCTTCAAGAACTCATGTTTAC
 GGGCTCTCATAAAGGACAGACCAAGTTTGTCCGCTCTTTCTGGGAAGATGGCTGAGACTACGGAACTTCTC
 CCAATGATGTCTCTCACTGAATCTTCTCCAAACCACTTCAGCAGCTTGTGTGTACCGGAATCTGCAAGTCCGCAAG
 AATTCCTATATGATGCCCTCTCTCAGCTTTGTCTGGAAGCTGTTGCGAACTTCGGAAGAGGCTTCCGCGAGGA
 AGACAGAATGGCGGGACAGAGATGGACATAGAATCCACGACGTGTCTCTATTACTCGGCAACCCCTGCAAG
 CTCTCTCATCTGGGCCATCTCTCAGATAAGAAGAACTCTCCAAAGTCAATTTGGGACAGACATCAATGCTGTGG
 ACTCTGGCAGCCCTGGGAGCCGACAGCTCTCGAAGACTCTGGCCAAAGTGGAGAACAGCATCAATGCTGTGG
 GAGGCTCCGAGGAGCTGGCTCTATGATACGAGACGACCGGCTGTTGAGCTGTTCTACTGAGTGTACAGCAGCATG
 AAGACTTGGCAGAACAGCTGCTGGTCTATCTCTGTGAGACTTGGGGTGGAGCAACTCTCTGGAGCTGGGGGTG
 GAGGCCACAGACAGCATTTCAACGCCAGCCTGGGGTCCAGAAATTTCTTTTAAAGCAATGGTATGGAGAGAT
 TTTCCCGAGACACCAAGAACTGGAGATATCTCTGTGTCTGTTTATATACCTCTTGGTGGCTGGCTTGTAT
 CATTTAGGAGAACTCTCTCGACAGACACAGAACTGCTTTGTATCTTGGTGGCTGGCTTGTAT
 GTGGCTCTCTCTCGAATGGATCTCTACTACCTGCCCTCTCTCTGTGTTTGTCTGCTGCTCATGGATTT
 CCATTCGGTGGCACCACCCCGGAGCTGGTCTCTACTCGCTGGTCTTTGTCTCTCTGTGATGAATGAGAC
 AGTGGTACGTANATGGGGTGAATATTTTACTGACCTGTGGAGTGTGATGGACAGCTGGGGCTTTTTCATCTC
 ATAGCAGGAATGTATTTCTGGCTCCACTCTTCTAAEAAAGCTCTTTGTATTTCTGGAAGCACTCAATTTCTGT
 GGACTACATTTATTTCTACTATAGATGATCCACATTTTACTGTAGCAGAACTTAGGACCCAGATTTATTA
 TGCTGCAAGAGATGCTGATGATGTGTTCTTCTCTGTCTCTCTTTGGGGTGGGATGCTGCGCTTTGGCGTG
 GCTCGAGCAAGGATCTTTAGGCAAGATGAGCAAGCTGGAGGCTGGATTTCCGTTCCGTCTGATACAGGCCCTA
 CCTGGCCAGTTCGGCCAGGTGCCAGTGACGTGGATGGTACCAGTATGACTTTGGCCACTGCACTGCACTCTG
 GGAATGAGTCCAGGCCACTGTGTGTGGAGCTGGATGAGCAAGCTGCCCGGTTCCCGAGTGGATCAGCATC
 CCGCTGGTGTGATCTACATGTTATGCAACCAACATCTCTGCTGTCAACCTGCTGGTGGCATGTTTGGCTACAC
 GTTGGGCAACCGTCCAGGAGAACTGACCGGCTTGGAGTTCCAGAGGTACTTCTGTGTGGAGGATGATGCA

19/162

FIGURE 17B

GCGCGCTCRATATCCCCCTCCCCCTTCATCTCTCTCGCTTACTCTCATATGGTGGTGAAAGAGTGCCTCAAGTGT
 TGCTGCGRGGGAAAAACATGGAGTCTTCTGTCTGCTGTTTCAAAAATGAGACACATGAGACTCTGGCATGGGA
 GCGCTGTCATGRAGGAAAACTACCTTGTCAAGATCAACACAAAAGCCAACGACACCTCAGAGGAANTGAGGATC
 GATTTAGACAACTGGATACAAAGCTTAAAGATCTCAGGGTCTTCTGAAAGAGATTGCTANTAAATCAAA~~AAA~~
 AACTGTATGAACCTCTAATGGAGAAAACTAATTTATAGCAAGATCATATTAAAGGAATGCTATGAACAAATTT
 GCTATCGACTACTAAATGAGAGATTTTCAGACCCCTGGGTACATGGTGGATGATTTTAAATCACCCCTAGTGTGC
 TGAGACCTTGAAGAAATAAGTGTGTGATTGCTTCATACCTTGAAGACGGATATAAAGGAGAGAAATTTCCCTTTAT
 GTGTTTCTCCAGRATGGTCCCTGTTTCTCTCTGTGTCTCAATGGCTGGGACTGGAGCTTGTATAGTTTAAAGTGTG
 TTCTTACCGCTCCCTTTTCTCTTAAATCTTATTTTGTGTGAACACATATATAGGAGAACATCTATCTCATGAAT
 AAGAACCTGGTCTATCTTTTACTOCTGTATTTGTTATTTGTTCAATTTCCAAATGTAGTTCTCTAGTTTCCCTTTT
 TGTATTTATGTGACTAAATAGTTGGCATATTTGTTAAAGTCTCTCAAAATAGGCGAGATCTTAAACATGCTGCA
 GCAAGAGACACCCCGCTCTCTTCAGGAAGAAGTGTCTTCTTCTCAGGATGCTCTTACCTGTCTGAGGGAGGGA
 CAGGGCAGTCTCTGTCTCTCTCAGGACTCACCGGCTCCTATTGAAGGAACCCGCCCATTCCTAAATATGAGAA
 AAGTCTGCCAAAATGCAACCTTGAAGGCACTACTGACTTTGTTCTTATTTGGATACCTCTCTTATTATATTT
 TTCATTTAAAAATATAGCTGGCTATTATAGAAAATTTAGGCCATACAGAGATGTAGAAAGAACATAAATTTGTC
 CCCATTACCTTAAGGTATCTCAGTCAACAAATTTCTGGATGGTTTTTCAAGTCTATTTTTTTCTCATGTATGTC
 TCAATTTCTCTTTCAAAATTTTACAGRATGTTATCATACTACATATATACITTTTTATGTAGCTTTTTCACCTTAG
 TATTTTATCAATATGTTTTTATTATTTTATAGCTTCTTAAACATTTATATCAATTAATGCATAAATAGGCAAC
 CTCTAGCGATTACCAATAATTTTGTCTCTTGAAGGCTATCTCGAGTTGATCATGGGATGAGCATCTTTGTGCAAT
 GAATCTATTTGCTGTATTTTGGGAAAATTTTCCAAGGTAGATTCCAATAATATCTATTTATTATTAAATATTA
 AAATATGAGATTTATTTATTAACCACTTTATAAGGCTTTTTTCATAAATGTATAGCAAAATAGGAATTTATTAAGT
 AGCTAAGATATGAGATACATGACCTGAACCTATTAATAAATATTTATATTAAACCTTAGTTTGAAGAGAG
 TCAATATGCTTATTTAAATATTTATGGATGGTGGGAGATCACTTGAGGTGAGGAGTTTCGAGACCGGCTGGCA
 ACATGGCAAAACACATCTCTACTAAAAATAAAAAAATTAGCTGGGTGTGGTGGTGCACCTCTGTAACTCCAGC
 TACTCGAAGGCTGAGGTACAAAGATTTGCTGGACCTGGGAGCGGAGGTTGAGGTGAACCAAGATTGCAACAC
 TGCACTCCAGCCGGGTGACAGAGTGGAGCTCCGACTGAAATTAATTAATAAATAAATAAATAAATAAATAA
 TAAATATTATGGATGGTGAAGGGAATGTATGAGATTTGAGAGATTTACTTGAACACCTGTAGTCCGAGCT
 TTCTCTGGAGTGGTGGTATTTGAGAGGATGTGCGCAAGGCANTTGAAGTCCCATATTTAGTTTCTCAGCTT
 TGAATACACTATAAATCACTGGGCTGAGAGGGAATTTTGAAGGAGCTACTTAAAGATCTAATTTGAAAAA
 CTACAAAACATTAACATAAAAAAGTTTATTTTCTTTGCTCGGAGTGTGATGANAATTAATCTACTCAGACAT
 CACTATGTTTGCAAGGAATTAACACAAATTAAGATGCTTTTTTACTTAAACGCCAAGCAGAAAACTTGGCCA
 ATACTGAGAGCACTTGCATTAGAGAGGGAACGTGTAAATGTTTTCAACCCAGTCACTCTGGTGGATGTTTT
 GCGAGTTACTCTGAGAAATTTTGTCTATGAAAATCTATTTTTTATGTTAGTGTACCTCACAATATGTTTGAACA
 CTCTATATCAAGGTGCTATGTCTTGTGTATGTTACTAATGTGTCTGTGACTTTTTCACACTGTGAGAACT
 CTGGCGCTTGGTTTAAATGAGTGTGTTCTATGAAATAAATAATGGAGGAATTTGTCAAAAAABAAAAA
 AAAAAAABAAAAAABAAAAAABAAAAAABAAAAAABAAAAAABAAAAAABAAAAAABAAAAAABAAAAA

FIGURE 18

[illegible]

21/162

FIGURE 19

GGGGCGGGGCGAGGTGAGGTGTTGGCAGTGGAAAGGGGTTGGGCTCGGGGGCGGGGGGGGCGGCGGAGCGGAT
 GGGCGCGCGCGCGCGAGGGGGGATAAAAAGCGGTGCGCTGCGAGGTGGGCGGGAGGGGGAGGGGGTGTCC
 GAGGGCGACAAAGAGTAGCAGGGGGCTGTACGAGCTGGTGTGGCGGGTGTCTGACGCGCGCTGCTGTGTGTGCAACDE
 CACGCTCACTCTCTGGCTCCGGCTTCGGGTTGGGTGCGACCTGGGAATCTGGGCGGGAGCTGTGTGCGCGCGCGCT
 CTGGCGGGGCTCTAGCGCGCGCTCGGGCTTCAAGCTCCGCAAGGCCCGCGAGCTGGGCGAGGAAGCGCGCGCACAC
 GGGACCGCGCGGGGGGGTGTGTGCTGGCAGCCGACACACCGAGTGGCGTGGCGCGGGGACGGTGTCTTCTT
 GGAGAACTGGCTGTGTGATATGGGCTTGGTGTACCGAGGTGGAGCAGGAACCCAGCTTCTCGGACCTGCGGAA
 GCTCTGTGGTGTGGTGTATGGCCGTGGGCTCTCTACATAGCGTCTACGACCCAGAGGTATTTTCARAAAGA
 AATAATTCAGATTTGGTGGATGAAATTTTAAACACACAGCAAGAACTTCTGGGCGTAGATTTTCARAAATPACTC
 ACCAGATTTTGCATATAGTAATGACAAAGAGATCAAGTTTAAATTTGCCATTTGGGCGTAGAGGTGTGTGTCTC
 CGAGAGATGGAAAGGCGATATTTGTAAAGCTGTCTAGGACTTTTGGCGATTTAGTAGCCAGAGCAAAAGGAGCA
 CCCACAGATTTGGATGTGATATGGTTAGCCAGTTTACTTAGTTCAAAATGTTGTCTGTATCTGATTTAGTATTT
 GAGTTCGGTCTCTGGGACAGCAATTAGGCTTTCTTCTCGGCGCATCAAGTTGTATGTGATTTGTCTTCTTTCG
 CTCTCCCACTTAAACATCAGTTATGAGGACTTTTCTCTCGCCCTCGTCATATGCGGCTGTGAGCAGCGCTGTG
 GGAAGCTAGTGTCTATTTGGTGTGATATTTGATTTGAGGCTTTGTGGAGGAGAGGAAACCAAGTGACTCTGATGTT
 TACAAAGACCTATGAAGCCCTGTACACACCTGTGAAGCCCTGTACACACCTAGTTCTATAATCCTCATATTTA
 TCAACAAACACAAAGAGTGTCTTACTTGAAGGTGAGTGTGTGCGGTGTGTGGCTGACACCTATTTGAGCACTTTGT
 NTGTGTGGAATAAACAAGTGGGGGCGCTGTGTGAGAGAGGAAATCATAGGCTCAACCTTTGACATATAGC
 ACTGATGTTTTAGGAGCTGAATGTGCACACTTAATAAGTCTTCAGCCCGACTACTTCCCTGTTTCTGGGGGGA
 GAAAGGGGCGCTGATTAGAATCTTCTGCTGTGTGTTTGGCGGGGAGGGAATAAATTTGTTCAGTCTTTCTTAC
 GACCAAACTTTAATTTTAGGAATAACATATGACTTACTGACCTGAAGCCTTTGAGTTGAAGAGAGCCCGAC
 AGAAGAGGACTCTGTGCTGTGCACATGTAAAGCTTCTGCTCACTTCAGAGCAGAGCGGAATACCTATCTGACG
 ATACCGCCCACTTTCATCTCTCTATATATAGCAACAGGTGTGACTTGAAGTGTGTCTCTGGTGTCTGTATTC
 TGGCTCTATGAGATTTATTTGAAGAGAACTCTTACTACATTTGAAATGCAAGCTTTTAAATTTAAATTTGGG
 TTGGCGAGTCAAAAGACCAAAAGGCTAAAGGCTAGTAAGTTTGAATCTTAAAGCTAAAGGTGGGAACTCA
 TTTAAATTTGAAGAAAGTTTGTATTTCTTTTGTATTTGATGGGCGATATGATATTAATTTAGAGTGTGT
 TTAATAAATCACTTCTCACTACTATTTTATTTAAATTAACATTTGAGGGAGTTTGAAGGCACTGATTTTCTC
 TCAAAAGTAACTGTCTCTCTTGTGGAGACACACTTTAGGGGCTATGGTTAATCTCGAGATTTATCTACGTR
 AACCTGATGTATACCGGTGTGAATAATCTTTAAGTAGGATTAAGGCGCTCTGTGGGGAATTAATGTACACAA
 AGCTTATTAATAAATAAATTTTACAATTTCTTTTATGACAGAGAGCAGCACTGTATCTGTATTTTAAAAATG
 AATAACTGATTTCTTGACAGGTGTTTAGATTTCTCTCCCTCACTGCTGATTTCTGGATAGAAACCTTTCTTTE
 ATTTGATAGACTCTTTTCAGAAACCTCTTATCAACAGGTGTACATATGTTATCAAACTGTACATTTAGAGT
 GAGGATTTAATATCTAGATCTCAGAAATTTGAATAATGCAAAAGAGCTGGATTTGGAAAGCATGTTCTACAA
 TTGCTGTGCAATCTGAGCTATGAGAGATTAATGTTTCAAGCTTTGGATTATGAAGCCCGGTTATGATTTTAA
 AATCACACTTTGAATTAATAAATGATTGAACTAATTTTGGTCCGGTGCATCATTTTGCATCGATGACCTTTA
 TACATTTGAAGTCTTTTGTTTTATTTTACTGTAGAGTTTCTCTGTGAGCTTACACATATCTAATCAGAGAA
 TTTCTGATTTGTCTTCTTATCTGTGATTAAGTATGATTAATTAAGCATTTGTAGTCAGCTTGAAGCTGATTTAT
 GCTTTTGTAAACATGATCGGTGTAAATGTCTTAATAACATCTGGAGTATGATTAACCTTTAATGAATGAATTT
 TATGGACTGATTAAATAAAGGATTTAATCTTTGTAAAGTGAAGTTAGTGGATTAATTTACGATGATTTGGA
 TATAGTCCAGTCAACAAAGCTTTAATATTTGCAATTTTGTGCTTTTATTTCTCTCTCTCTCTCTCTCTCTCT
 ACTTGAAGACATCTGTAGCTTGTAGCTTGTAGCTTGTAGCTTGTAGGAGGCGCAACTACAGACTACAGCTAG
 GATTCGATTTGATTAAGTACCTTCCAGATTTCTCTCTTACGAGTTTCACTCTGATATGATTTCTCCCACT
 TGAATGGCCCTTGGTGTCTGTAAATGCTGCGCAAACTCATCAAGCTCTACGCTCAAGGCTCCCTTTGGAC
 TCCCAAGAGCACTGTTCTTTTAAACAAAGGTGTATGCTTTTATTTGATTTGGAATAATTTGCTTTTAAATTTG
 TTTCTGTTGCAACTTCCCACTGGAAATTAACAAATTAACAAATTAACAAATTAACAAATTAACAAATTAACAAAT
 GCAAGATTTTGAAGGATTTGAATTCATTTCCAGATTTCTATTTGCTTTTGTCTTATTAATATATATATTTGAT
 TACTGTATTAAGTTTAAAGGCTGTTTAAATGATAGCAATTCGGATATTTGTGATTAACGCTTGAAGAA
 TCCCTCTCTTTGGAGGAGGCTGTATATATATTAATCAACAGTGGCAAACTCACTGCTCACTATCACTATTTAA
 CTCTTGAATGTTGTATGAGATTTGACACCATGTACTATGCTGTAAAGCAAGTTTATGATTTAGGAATCA
 ACTTGTGATGTTTGTATGAGATTTGACACCATGTACTATGCTGTAAAGCAAGTTTATGATTTAGGAATCA
 AATTTTGTGATTTTATTTTGAAGTTTGAAGTTTGAAGTTTGAAGTTTGAAGTTTGAAGTTTGAAGTTTGAAGTT
 TTTCTTGAATTAATAAAAAAGGCCCGCGGTCCGC

22/162

FIGURE 20

GAGGTGAGGTGTTGGCAGTGGAAAGGGGCTTGGGGCTCGGGGGCGGGGGGACGGCGAGCGATGGCCCGCGCCG
 CCGCAGGGGGCGGATAAAAGCAGCTCGCGCTCGCGGAGTGGGCGGGAGGAGAGGGGGTGTCCGAGGGGCCACAAG
 AGTATGACGGGGCTGTACGAGCTGGTGTGGCGGGTGGCTGCACGCGCTGCTCTGTCTGCACCGCAGCTCACTC
 CTGGCTCCGGGTTGGGTCGGCACTGGAACCTGGATCTGGCGCCGCTGCTGCGCGCGCGCTCTGCCCGCTCC
 TAGCGCGCTCGGCTTACGCTCCGCAAGCCCCCGGCACTCGGCAGGAAACCGCTTCCACCGCGGCAACCGCGC
 GGGGGGCTGGTGGCTGGCGCGCGCACACCAACCGGATCGGCTGGCGCGCGGACGGTGGTCTCTGGGAGAGCTGG
 TGTGCATATGGGCTGGGTGATCACCGAGGTGGAGCAGGAACCCAGCTTCTCGGACATCGCGAGCCTCGTGGTGT
 GGTGATGGGATGAAATTTTAAACACACAGCAGAACTTCTGGGCTAGATTGTTCAAAATACTCACCGAATTTGC
 AAATAGTAAATGACAAAGATGATCAAGTTTTAATTGCCATTTGGCAGTGAAGGTGCTGTCTCGGAGATGGAA
 AAGCAGATTAFTGTAGAGCTGCTCAGGACTTTTGGCAGTTAGTAGCCGAGAGCAAAAGAGACCCACAGATTTG
 GATGTGATACGTTAGCCACTTTACTTAGTTCAAATGGTTGTCCTGATCCTGATTAGTATTGAAGTTCGGTCC
 TGTGGACAGCACATTAGGCTTCTTCCCTGGCACATCAGATTGACTGAGATTGTCTCTTTGGCTTCCACCTAA
 ACATCASTTAGGAGACTTTTTCTCTGCCCTTCGTCAATATGCAGCCTGTGAACAGCGCTCGGGGAACTAGTGG
 TCATTGGTTGCA

26/162

FIGURE 24

CCGCCAGGTCCTTCGGCAATGAACCTTCUACCAGCAGGAGCAGGCTTCGGCTACGACCGGGAGTTCCCTCCGCAC
CCTGCCCCGGGCTTCCTCATCTGTTGGCCGAGATCGTTCTGGGGCTGCTGGATATGGACGCTTATTGCTGGAACTFGAST
ACTTCGGGGTCCCCGCATTTGGGCTGGGTCATGTTTGTAGCTGTATTTTACTGGGTCCTCACCGCTCTTCTTCCTC
ATTATCTACATACAAATGACCTACACCAAGGATCCCCAGGTGCCCTGGACAACAGTGGGCGCTGTCTTTACGG
CAGTGCCCTCGTCTTGATACCTCTCTGCCCCGCTGTTGTAGATGCACTCTCCGCTCTCCCGTGGAGGGGACAGTCACA
ACTTCACACAGCTGGGGGGCCCTCATCGTTCTTTGGCTTCCTGGGTCAACATCTGCTACGCTGGAAATACATATTTC
AGTTTTATAGCATGGAGATCCAGGACCATACAGTCGATTTTACCATTTTGATTAATTAAGGAAAAAAGGAAG
ACTCTCACTGTAAAAACAGCTGTAGGTAAATGTATATCCAGAGAACTGTATTTAACTAATTAATGTTTTTT
ATATTCCTTAAATTTGCTCACAAATTTGTGCTTCTTACAAATTAACCTGGATACTTATTTGCAAGTGTGTAGCT
TATAATGAACTCTTAAGTATCTTATTAATGTATTAACTCTTCATAGATCATATTTCTTAGACATGTTTAAA
TAGATAAATTTGCTAATATTGAGAAATGTGTCAAGTTTGTAAACCTAACTTTTAAAGATGACAGATTCTTTTTGTAT
TAAATCTTGCAAATCCCAAAAAAAAAAAAAAAAAA

27/162

FIGURE 25

GCCTTTGGCAATGAACTTCTCCACAGCAGCAGCAGCTTCGCCTACGACCGGGAGTTCCCTCCGCACTTGCCCG
GCTTCCTCATTCCTGGCCGAGATCGTTCTGGGGCTGCTGGTATGGACGCTTATTGCTGGAACTGAGTACTTCGG
GTCCCCGCAATTTGGCTGGGTCAATGTTTGTAGCTGTATTTTACTGGGTCCCTCACCCGTCTCTTCCTCATTTATCTA
CTAACAATGACCTACACGAGGATTCGCCAGGTGCCCTGGACACAGTGGGCCTGTGCTTTAAGGCGAGTGCCT
TCGCTCTGTACCTCCTGCGCGCTGTTGTAGATGCACTTCCGTCCTCCCTGAGACGGACAGTCACCACTTCAAC
AGCTGGGCGGCTCATCGTTCTTTGCCCTTCTGGTCACCATCTGCTACGCTGGAAATACATATTTCAGTTTAT
AGCATGGAGATCCAGGACCATCACAGTGAATTTACCAAGGGC

28/162

FIGURE 26

GGCCCTGCCCTGAAGSCTGGTCACTTCGAGAGGTAAATCCCCCTCTTTGACTTCTGGCCAGSGTTTGTGCTGAG
CTGGCTCGAGCGCGCTCTCAGGCCTCGCTCCGGGACGCTCGGGCGGCCTCGGGCCCTCCTGCCTCGAGGATCAGGC
CCACACCGSTGACGATGTCTCGAGCATGGAGGGGAGTTTCACCTTTTCCAGAAAGCAATGTTTTTCCTCTTG
GCTCTGCTCTCGGCTACCTTCGCGCCCATCTACGTGGGCATCGCTCTCTCGGECTACCCCTGACCACTGGTG
CCGGAGCCCCGAGTGGACGAGCTGAGTCTGCGCTGCGGCTGGAGTCTCTGCGAGGAACTGAACTACACGGTGGC
CGGGCCAGGACCTCGCGGCGAAGCCTCCGCCAAGACAGTGTAGGCGCTACGAGGTGAGCTGGAAACGAGGACCG
TTTGACTGCTTGGACCCCCCTGGCCAGCCTGGACACCAACAGGAGCGCGCTGCGCACTGGGCCCCCTGCCGGAGCGG
CTGGGTGTACGAGACGCGCTGGCTCGTCCATCGCTACCGAGTTTAACTGCTATGTGCCAACTCCTGGAGTGTGG
ACCTATTCCAGTCACTAGTGAATGTAGGATCTTTATTGGCTCTATGAGTATCGGCTACATAGCAGACAGGTTT
GGCCGTAAAGCTCTGCGCTCCTAACTACAGTCTCTATAAATGCTGCAGCTGGAGTTCTCATGGCCATTTCCCCAAC
CTATACGTGGATCTTTAATTTTTTCGCTTAATCCAGGACTGGTCAGCAAGCAGGCTGGTTATAGGCTACATCC
TGATTAACGAATTTGTTGGGCGGAGATATCGGAGAACAGTGGGGATTTTTTACCAGTTGCCTATACAGTGTGG
CTCTGGTGTGATGCTGGGGTGGCTTACGCACTTCCCTCACTGGAGGTTGGTTGCACTTCCAGATTAAGAAATGCTG
CTTCTCTCTCTGCTCTATTACTGGTGCATACCTGAGTCTCCCAAGTGGCTGATCTCCAGAAATAGAAATGCTG
AAGCCATGAGATCATTAAAGCACAATCGCAAGAAATGGAAATCTCTACCGGCTCGCTTCAGCCCGTGA
CTTGAAGAGGAAATCGGCAAGAARTTGAACCTTCAPICTCTTGACTTGGTCAGAACTCTCAGATAGGAAACA
TACTATGATATTGATATACACTGGTTCAGGAGCTCTGTGCTTACCGAGGCCCTCAKCAAGCACATGGGCTTG
CAGGTGACAAATATCACTGGATTTCTTCTACTCTGCGCTGGTTGAATTCCLAGCTGCGCTCATGATCATCTCC
ACCATCGACCGCTCGGAGCGCGTACCTTGGGCTGCACTCAATATGTTTGGAGGGGCGAGCTGTCTGGCCCT
AGTTTTATACCTGGTGATCTACAAATGGCTAAAAATTTATTTCTCATGCTTGGGAAGATGGGATCAATGG
CCTATGAGATAGTCTGCGCTGGTCAATGCTGAGCTGTACCCCAATTCATTTAGGAATCTTGGCGTCCACATCTGT
TCCCTCAATGTGTGACATTGGTGGCATCATCAGGCCATTCCTGGTCTACCGGCTCACTAACATCTGGCTTGA
CCGCTGTATGCTTTTGGGCTACTTGGCTTGGTGTGTGGAGGCTCTGGTGTGTGTGTCCAGAAATTAAGGGA
AAGCTTTGGCTGAGACCATCGAGGAGGCCGAAATATGCAAGACCAAGAAAAATTAAGAAAGATGATTTAC
CTCCAGTTCAGAACTAGACATTTCCATTGAATGAAGAGAGAGACCGTTGCTGCTCATGACCTAGCTTTGA
TGGCAGCAGAGCCAAAGTAGAAATCCCTGCACTCATCAAGGCCCTACAACTCAGCAAACTTACCCCTGA
GCCCCATACAGCTAGGTCTACAGCCAGTGGAGCTATTGTGACCTGTGGAAATATACCATGGGACAGATCCT
GCCAAATTTCTCCAGCTCATCTTTATCTCAGCATTCCTAGGACATTTGACATTTCTGGAGGGTTTTTTT
TCCGATCTTGTATTTTTTTAATTTGATCTTTCTTTGCAATGCTAGCACCAGAAATACATAGGAGACTGT
GGGCTAGGCARAAAAATAGAAAAAGTGTGAATAACAGTAAAGTTGGAGAGGAGCATCTATTTTCTTAAGAA
ATAAARCBCCNAAACAAAAAATAAAAAA

29/162

FIGURE 27

GCCCTTCTCCTGCTGAGGATC**ATG**CCACCCGCTGGAGCATGCTCTGGAGCATGGAGGGAGTTTCACTTT
 TTCCAGAGCAAAATGTTTTTCCTCTTGGCTCTGCTCTCGGCTACCTTCGCGCCCATCTACGTGGGCATCGTCTT
 CCTGCGCTTCAACCCCTGACCAACCGCTGCCGGAGCCCCGGAGTGGCCGAATCTGAGTCTGCGCTGCGGCTGGAGTC
 CTGCGAGGAGACTGAACTACACGGTGGCGGGCCAGGACCTGCGGGGGAAGCTCCCCBAGACAGTGTAGGCGC
 TAGAGGTTGGACTGGAACCAAGCACCTTCGAGTGGCTGGACCCCCCTGGCCAGCTGGACACCAACAGGAGCCG
 CCTGCCACTGGGCCCCCTGCCGGGACGGCTGGGTGTACGGAGACCGCTGGCTCGTCCATCGTCACCGAGTTTAAAC
 TGGTATGTGCCAACTCCTGGATGTTGGACCTATTCCAGTCAATCAGTGAATGTAGGATTCTTTATTGGCTCTATG
 AGTATCGGCTACATAGCAGACAGGTTTGGCCGTAAAGCTCTGCTCCTAACTACAGTCTCTATAAATGCTGCAGC
 TGGAGTTCTCATGGCCATTTCGCCAACCTATACGTGGATGTTAATTTTTTCGCTTAATCCAGGACTGGTCAGCA
 AAGCAGGCTGGTTAATAGGCTACATCCTGATTACAGAATTTGTGGGCGGAGATATCGGAGAACAGTGGGGATT
 TTTTACCAAGTTGCCATACAGTTGGGCTCCTGGTGCTAGCTGGGGTGGCTTACGCATTCCTCAGTGGAGGTG
 GTTGCAGTTCAAGTTTCTCTGCCCCAATCTCTCTCTTCTTGCTCTATTACTGGTGCATACCTGAGTCTCCAGGT
 GGCTGATCTCCAGAATAGAATGCTGAAGCATGAGAACTATTAGCACATCGCAAGABAAATGGAATATCT
 CTACCGGCTCCCTTCAGCCCTGAGACTTGAAGAGGAATCTGGCAGAAATGGAACCCCTCAATTTCTTGACTT
 GGTCAAGACTCCTCAGATAGGAAACATACTATGATTTTGATGTACAACTGGTTCTCAGAGCTCTCTGCTCTAAC
 AGGGCCTCATCTGCACATGGGCCCTTGCAAGTGACAAATATCTACCTGGATTCTCTCACTCTGCCCTGGTTGAA
 TTCCCGAGCTGCCCTCAFGATCATCTCACCATCGACCCGATCGGAGCCGCTTACCTTGGGCTGCATCAATAT
 GGTTCAGGGGCGAGCTGTCTGGCCTCAGTTTTTATACCTGGTGAATCTACATGGCTAAABANTATTAATCTCAT
 GCTTGGAGAGAAATGGGGTTCACAAATGGCTATGAGATAGTCTGCCGCTCAATGCTGAGGCTTACCCACATTC
 ATTAGGAATCTTGGCTCCACATCTGTTCCCAATGTGTGACATTTGGTGGCATCATCAGCCATTTCTGGTCTA
 CCGGCTCACTAACATCTGGCTTGAGCTGCCGCTGATGGTTTCGGGCTGCTTGGCTTGGTGGCGAGGCTTGC
 TGCTGTTGCTTCCAGAACTAAAGGGAAGCTTGGCTGAGACCTCGAGGAGGCCGAANATATGCAAGAGCCA
 AGAAAAAATAAGAAAGATGATTTACCTCCAAATTCAGAACTAGACATTCATTGAATC**AGA**AGAGAGAGCC
 GTTGTGCTGTCATGACAGGGC

30/162

FIGURE 28

CGGGCCAGGTTTCAGAGCTCGGCGCGCGCTCCATCCCGACCCCTGCGAGGGAGCGCTGACCATGGCTCCCTG
 GCGTGAATTGGGAGATTGCCAGCCCAACCCCGATAGTACCTCGAAGGGGCGCGAGGTCAGCAGCCCACTGGCC
 CTGATTAAGAGCAAGAGAGACCAACAAACAGATAACACTGAGGCGACCTGTAAACAGAGATTGAACCTTCTGCGCTC
 TACTCCACAGGCTACACTGATAGATGAGGCCCACTGAGGTGGATGACCCCTGGAACCTACCCACTCTTCGAGACTC
 GGGGATCAAGTGGTCAGAGAGAGACACCAAGGGGAGACATTCTCTGTTTCTTCCAGGGGATTGGGAGATTGATTT
 TACTTCTCGGATTTCTCTACTTTTTCTGTGCTCCCTGGATATTTCTTAGTAGCGCTTCACAGCTGGTTGGAGAA
 AAAATGGCAGGACAGTTCTTCAGCACAGCTCTATTATGTCACCCCTTTGTTGGGGCTGGTGATCGGGGTGCT
 GGTGACCGTCTTGGTGCAGAGCTCCAGAGCTCAACGTCCTACGTTGTGACGATGGTGTCTCTTCACTTGCTCA
 CTGTTCCGGCTGGCATCCCATTAATCATGGGGGCCAACATTGGAACGTCACACCCACACTATTGTTGGGCTC
 ATGCAAGTGGGAGATCGAGTGGATTCAGAGAGCTTTTGCAAGAGCCACTGTCCATGACTTCTTCAACTGGCT
 GTCCGTGTTGGTCTCTTGCCCGTGGAGGTGGCCACCAATTACCTCGAGATCATACCCAGCTTATAGTGGAG
 GCTTCCACTTCAGAGATGGAGAGATGCCCGAGTCTTCGAAAGTCATCACTAAGCCCTTACAAAGCTCATTT
 GTCCAGCTGGATAAAAAAGTTATCAGCCAAATTGCAATGAACGATGAAGAGCGAAAAACAGAGTCTTGTCAA
 GATTTGGTGC AAAACTTTTACCAACAGAGCCAGATTAACTGCTCACTGTTCCCTCGACTGCTAACTGCACTCC
 CTTCCTCTGTTGGAGCGGATGGATCCAAAATCGGACCATGAAGAAATGTACCTCAAGAGAGAACATCGCCAA
 TGCCAGCATATCTTTGTGAATTTCCACCTCCCGGATCTTGTGTGGGCAACATCTTACTCATCTCTCCCTGCT
 GGTCCCTCTGTGGTTGCTGTGATCATGATGTCAGAGTCTTGGGCTCTGTGCTCAAGGGGCGAGTCCGCCATGTG
 TCAGAGAGACCATCAACACTGATTTCCCTTTCCCTTTGCTATGTTGACTGGCTAGCTAGGCGATCTCTGCTGGG
 GCAAGGATGACCTTCATGATACAGAGCGAGCTCTGTGTTGACGTCGGCCCTTGACCCCTGATTTGGAATCGGCT
 GATTAACCTATTAGAGGGGCTTATCCACTACGCTGGGCTCCACATCGGCACACCCACCCGCCATCCCTGGCGG
 CCTTACAGAGCCCTGGCAATGCATTGAGGAGTCACTCCAGATCGGCCCTGTGCCACTTTTCTTCAACATCTC
 GGCATCTGTGCTGTGGTACCGGATCCGGTTCACTCGGCTGCCCATCCGATGGGCCAAGGGCTGGGCAACATCTC
 TGCCAGATATGCTGATTCGCGCTCTTACCTGATCATCTTCTCTTCTGATCCCGCTGACGGTGTTTGGCC
 TCTGCTGGCCGGCTGGCGGCTGCTGGTTGCTGTGGGTTCCCGTCTGTTTATCATCATCTCTGTTACTGTG
 CTCGACTCCTCAGTCTCTGTCGCCACGGGTCTGCGGAGAAACTCCAGACACTGGAACTTCTTGGCGCTGTG
 GATCGCTCGCTGAAGCCCTGGGATGCCGTGCTCCAAAGTTACCCGGCTGCTTCCAGTGGCTGCTGCTGCTACT
 GCTGCCGCTGTGCTGCTGCCGCGCTGCTGCTGCTGTGTGCTGCTGCCCAAGTGTGCTGCTGCTGAGCAGTGTGCTG
 GAGGACTTGGAGGGGGCGCAGGAGGGGGCAGGATGCTCCCTGTCAAGGCTCTGAGACCTTTGATACATAACTAT
 TAGCAGAGAGGCTCAGGGTGAAGTCCCTGCCCTCGGACTCAAGAGCGGATGCAAGGCTGTAGGGGAGCGCCC
 AGATTGTGAGGATGGGGGATGGTCTTGAATTTTGTGCTGCTCTCTCCCTCCACTCTGTGACCCCTTCAAC
 AACTCGGAGAGATTGCTCCCATTAGCGAATGAATTTGATGCACTCTAAAAAAAAA

32/162

FIGURE 30

GGCGTGGGAGCTGCCCTAGGCCGGGCCCCCTGCCAGGGAGCAGTCTGCATCGCAGAGGCGAGGGCAGACTGGCTCC
TCACAGCCTGAGAGCTCATCTCTCTGCACGGGCCAGGCCAGGCCAGCAGAGGACCCAGGGCAGCAGTGCACACA
GGTCCCCGGGGACCCGCCCATGGTGGAGCGGATGGTGGGTGTGGGCCCTTGTGGCCGCTCTGCACCTGCAGACTTCT
TTCGGGACCGAGGACAGAGGGATCATGAGGGAGCTCCCCCTGTCATTGATGGGCAATGACCTCCCCCTGGCAGCTG
CTGGATGTGTTCAACAACCCGGCTCCAGGACAGAGGGCCAACTGACACCTTGGCCGGCACACACACCAACAT
CCCCAAGCTGAGGGCCGGCTTTGTGGGAGGCCAGTTCTGGTCCGTGTACACGCCCTTGGACACCCAGACAAAG
ACGCCCTGCGGAGGACGCTGGAGCAGATGACGTGGTCCACCGCATGTGCCGATGTACCCGGAGACCTTCTCTG
TATGTCACACAGCAGTGCAGGCATTGGCCAGGCCCTTCGGGAGAGGGAAGGTGGCCAGCCTGATCGSCGTGGAGGG
CGGCCACTCCATTGACAGCAGTTTGGGCGTCTGTGGGCACTCTATCAGCTGGGCATGCGGTACCTGACCCCTCA
CCACAGCTGCAACACGCCCTTGGGCTGACAACTGGCTGGTGGACACGGGAGACAGCGAGCCCAAGACCCAGGCC
TGTCAACCCCTTGGGCAGCGTGTGGTGAAGGAGCTGAACCGTCTGGGGGTCTCATCGACTGGCTCAGCTGTC
TGTGGCCACCATGAAGGCCACCCCTGCAGCTGTCCAGAGCCCGGTCATCTTCAGCCACTCTCTCGGCCCTACAGCG
TGTGCGCAAGCCGGGCCCAACCTGCCTGACGACGTCTGAGGCTGGTGAACAGACAGACAGCCCTGGTGTGGTGG
AACTTCTACACAAATTACATTTCTGCAACCAAGAGGCCAACCTGTCCCAAGTGGCCGACCATCTGGGATCACAT
CAGGAGGTTGGCAGGAGCCAGAGCCCTGGGTTTTGGTGGGGACTTTGATGCTGTTCCAGGGTCCCTGAGGGG
TGGAGGACGCTCCAAATATCCAGACCTGATCGCTGAGCTGCTCAGGAGGAACTGGACGGAGGGCGGAGGTCAG
GGCGCACTGGCTGACAACTGTCTGAGGGTCTTCCAGGCTGTGGAAACAGGCCAGCAACCTCACACAGGCTCCCGA
GCCCTCATCGCCACTGGGGGCTCCTGCTGGCCCTCCCTCGCTCCCGTGGTCCCTGTCTGTCTCTCTGTGAAC
CTGGGAGACCCAGAGTCCCCCTTAGGGTTCCCGGAGCTCCGGGAAGACCCGCCCTCCAGGACTCCAGTGGCA
GGAGCCCTGTGCGCCACATGCAAGGACCAAGCTCTCTGAGAGGACGCTGGGCTTACCTGGGGGGCAGGATGC
CTGGGGACAGTTCAGGACACACACACAGTAGGGCCCCCAATAAAGCACAACCCCTTCANAAAAAANAAAAA
AAAAA

33/162

FIGURE 31

CAATCAAAGCCTCCTCAGCCTTCTGAGTCAGCCTGAAAGGAAACAGGCCGAACCTGCTGTATGGGCTCTACTGCCA
GTGTGACCTCACCCTCTCCAGTCACGCCCTCCTCAGTCCAGCTATGAGTTCCCTGCAACTTCACACATGCCACCT
TTGTGCTTATTTGGTATCCAGGATTAGAGAAAGCCCATTTCTGGGTTGGCTTCCCCCTCCTTTCCATGTATGTA
GTGGCARTGTATTGGAAACTGCATCGTGGTCTTTCATCGTAAAGACGGAACGCAGCCCTGCACGCTCCGATGTACCT
CTTTCTCTGCATGCTTGCAGCCATTGACCTGGCCTTATCCACATCCACCATGCGCTAAGATCCTTGCCCTTTTCT
GGTTTGATTCGCCAGAGATTAGCTTTGAGGCCCTGTCTTAACCCAGATGTTCTTTATTCAEGCCCTCTCAGCCATT
GAATCCACCATCCTGCTGGCCATGGCCTTTGACCGTTATGTGGCCATCTGCCACCCACTGGCCATGCTGCAAT
GCTCACAATAACAGTAAACGCCCCGATTGGCAFCGTGGCTGTGGTCCGCGATCCCTCTTTTTTTCCCACTGC
CTCTGCTGATCAAGCGGCTGGCCTTCTGCCACTCCATGTCCTCTGCACTCCTATTGTGTCCACCGAATGTA
AAGAASTTGGCCTATGTCAGACACTTTGCCCAATGTGGTATATGTTCTTACTGCCATTCTGCTGGTCATGGGCT
GGACGTAAATGTTCACTCCTTGTGCTATTTTCTGTGATAATACGAACGCTTCTGCACTGCCCTCCAGTCAGAGC
GGGCCAAAGCCCTTTGGAACTGTGGTGCACACATTTGGTGTGGTACTCGCCCTCTATGTGCACTTATTTGGCCTC
TCACTTGTACACCGCTTTGGAAACAGCCCTTCATCCCATTTGGCGTGTGTCTCATGGGTGACATCTACCTGCTGCT
GCCCTCCTGTCACTCACTCCCATCATCTATGGTGGCAAAACCAACAGATCAGAAACAGCGGTCTGGCTATGTTCA
AGATCAGCTGTGACAGGACTTTGCAAGGCTGTGGAGGGCAAGTGAACCTTAACACTACACTTCTCCCTATCTTTA
TTGGCTTGATAACATATATTTCTAACACTAGCTTATTTCCAGTTGCCCATAGCACATCACTACTTTCTC
TGGCTGGATGTAACTAAGTATGTATCTCTACCTAAAGGCTATTATGTGGATAATACATACTAATGAA
GTATTACATGATTTAAAGACTACATTAACCAACCAACATGCTTATACATTAAGAAAAACATAAGATACATGA
TTGAAACCAAGTTGAAAAATAGCATATGCCCTTGGAGGAAATGTGCTCAAAATTAATGATTTAGTGTGTGCC
TACTTCTCTCTCTTTTTTCTTTCTTTTTTTTTTATGTGGTGTAGCTGTCACTACAACTTTTTTTTTTTTTGA
GATGGGCTCTCCAGCCTGGGCCACAGAGCARGACCTGTCTCAAGCATAAAATGGATATACATATCAAAATGAA
ACAGGGAABATGAGCTGACATTTTATGGGAGCCA

35/162

FIGURE 32B

TGGATT CAGACACCCACGAAACAGTCTTATGGATCAGATATATCCAAATCTCATACTCACTATCTGAGATTCG
 AAGACGAAATACGAGTCACAGAGGTATCTCAGACAGTCANACTGGTATGGACAGAGAGCTCGGTAAATCACC
 TCAGCAATGGGCTATCTCCAAAGACCAATGATGGAAAGAGGAAATGACATTCAGAGCTGGTAGTGCCTGCT
 TCTCTCAGGCTCTGAATCTAAAGCATGGGCACTCTGACAAAGTGTGAGAGAAAGTGGATCAGGACAGGATACCT
 CAGATAGGCTTATATGAGATGAGACCTTCCACAGATTCAGTCTTTCGACAGCTATATGAAAGAGAGTCTGATGGG
 ATCTCTGGACAGAGTGTACTCAGAAATTAACCTCTGATATCCACAGTCCCAACAGTCATCTGTACTACCGAGAA
 CTGAGAGTGTTCACAGCTTTCAGAGGACAGAGGCTGATATAGTACGACATGAGTCTCGTATTTGGGTCTAGCTGAGG
 GGTGGAAATCCGAGAGAGAGGCTATATACCCCTTGTGATCTGTCGAGCCCTGACTTTTATCTGCTCTAGCTGTT
 CTCTGTGGTATTTCTCATCTACTGGAGAAATGCTTCCAGACTGCACACTTTTACTTAGAGGACAGTACATACCCC
 TAGACTTATATCCACACTCCCAACACTTATCTTTCCAATTTGAGATGATCTCGGAGCAATTCCAATTAAGCACT
 TTCCAAAGCATGTTGCAGATTTTACATGCAGTGTGGGTTTACTGAGAAATTTGAGACATCGAAGAGGTTTTAC
 CAGGAAGTGCAGAGCTGTACTGTTTCACTTAGGTATTCAGACACACAGCTCCAACTACCCAGACACACAGCACAA
 GAKTCGATACATTAATCTGCTGCCCTATGATCATAGCAGGGTTAAGCTAGCACAGCTTGCCTGAARAGGATGGCA
 NACTGACTGATATATCATAGCCCAATTTATGTTGATGCTACACACAGACCAAAAGCTTATTTTGGTCCCGAAGGC
 CCACTGAAATCCACAGCTGAGAGTTTCTGGAGAAATGATTCGGCAACATATGTCGGAGTTTATTCATGATAC
 AAAGCTCTGTGGAGAAAGAGGAGGAGAAATGTGATCTGCTGCTGCCCTGCCATGGGACTGAGGAGATAGGAACT
 TTTCTGTCACCTCAGAGAGTGTGCAAGTCTTGCCTTTTAACTCTGAGGAAATTTTCTCTAAGAAACACAAAA
 ATAAAAAAGGGCTCCCAAGAAAGAGAGACCACTGGACCTGTGGTCAACAGATCTCACTACACGCACTGGCTGA
 CATGGGAGTACAGAGTACTCCCTGCCAGTGTCTGACCTTTGTGAGAAAGGCAGCCCTATGCCAAGGCCCTGAG
 TGGGGCTGTTGTCTGCTCCACTGCGACGTCTGGAGTTGGAGAAAGCAGGCCATTTATGTTGCTAGAGATGATGTTG
 CAGCAGATTCACACGAGAGGAACTGTCAACATATTTGGCTCTTAAACACATCCCTCCACAAAGAAATATTT
 GGTACAACTCAGGAGCAATATGTCTTCATTCAATGATCACTGTTGGAGGCCATCTACTAGTAAAGAACTCAGG
 TGTGTCAGACGTCATATTCATGGCTATGTTAATGCACTCCTCACTTCTGGACAGCAGGCAAAACAAAGCTAGAG
 AAACAATTCAGAGCTCCCTGAGCCAGTCAATATACAGCAGAGTGACTATTCGCGAGGCCCTAAGCAATGCAACAG
 GGAAGAAGATCGAATCTCTCTATCATCCCTGFGAAAGATCAAGGGTTGGCATTTCACTCCCTGAGTGGAGAG
 GCACAGACTACATCAATGCCCTCTATATCATGGGCTATTACAGAGCAATGAATTCATCAATTTCCCGAGCCCT
 CTCTTTCATACCATCAAGATTTCTGGAGGATGATATGGGACCATATGCGCAACTGGTGGTATGATTCCTGA
 TGGCTCAAAACATGGCAGAGATGAATTTGTTTACTGGCCAAATAAAGATGAGGCTATTAATTTGAGAGGCTTA
 AGGTCACTCTTATGGCTGAAGAACACAAATGTCTAECTAATGAGGAAAACTTAATTAATCAGGAATTTATCTTA
 GAGCTACACAGGATGATTATGTACTTGATGTGAGGCACTTCAGTGTCCATAAATGGCCAAAGTCAAGATAGCCC
 CATTAGATAAACTTTTGAATCTTTAAGTGTATAAAGAGCAAGCTGCCAATAGGGATGGGCTATGATGTTCTC
 ATGATGAGCATGGAGGATGACGGCAGGACTTCTGTGCTCTGACAAACCTTATGCACTACTAGAAAGAGAA
 AATTCOGTGGATGTTTACAGGCTAGCCAGATGATCAATCTGATGAGGGCCAGGATCTTTGCTGTGACTTGAGCA
 GTATCAGTTTCTCTCAAGAGTGTCTCAGGCTTGTGAGCAGCAGGSCAGGAGAGAGATCCATCCACTCTCTGG
 ACGAGTGGGTCGACAGTTCCTGATGGAAATATAGCTGAGAGCTTAGAGTCTTATGTTTAAACAGAAAGGGG
 TGGGGGAGTCACTCATGAGCATTTGTTTCTCTTCTTAAATTAGGCAGGAAATTCAGTCTAGTTCTGTATTC
 TGTATTTTCCATCACCCTGACAGTAACTTTCTAGACATAGGATTCGCGCCAAATTTATATCATTTACAAATG
 TGTGGCTTTTTCGAGACTGTGTAATTTACTTATATGTTTGAATCAAAATGATTAATTTTACAGATTTCTTA
 CAATGGAATTTGGTATTTTCTGTATTTGATTTTAAACAGAAATTTCAATTTTACAGAGTTAGGAATTCOA
 ACTACAGAAAGTGTGTTTGTGTTTGTGTCAAAATTTTGTGCTGATTTGTAGCAATATCAGGTTTGTCTAGAAAT
 TACTCTTATATCAGTACGCTCTGAATAAACACTCTCCATATGATATTTAGTGTGTTTGTATTTAGCTATGAGTATC
 ACCTTAAGATGAAGATACCTGTACTATGTGAAATACGCGCTAGTGTCTCATGAGGACAAATTTATGATTTAT
 AATTTAGTATTTTATATTTTACTGACTGAGTCAAGTGTTCAGTCTGTGTATTTTGTGTTTATTTAGCTATGAGTAT
 TCTATAGCTGGTCTACTCTACACAGTTTCTGACATTTGATTTGGTACCTAGTCAATTAACCTTGTGTTCTCAGC
 ATGATATTTTACTTTTGGAGAAATAGAAATACCTTCAATTTGAAGAGAGTTTCTATGAGATTAACACCTTAC
 CAACATTTGTCAAAATGTTTATCCAGGAAATGCAAAATATATATATATGTCATTAAAGAAAAA
 AAAAAA

37/162

FIGURE 34

ACGCGTGGGCCCACGCTCCGCCACGCTCCGGTCGGGGCCAGAGGCGAAGTGTACCTGGGGGCCCTGCTGGG
 GCACTGTAGCTGACGTCGCGAGATCCTGGAGCTGGCTGGCAACCCGCCCCGCGACAGAGACCCCGCATCATCTTGGCGCC
 ACCTGTAGCTGGCCATTTCGCRACCGCGGAGGAGCTTAACAGGCTGCTGGGCGAAGTCACCATCGCGCAGGCGGGT
 GTCCTGCCCAACTTCAGGGCGTGTCTCTGCCCCAGAGACCAAGAGCCACCCACAGGCCAAGGGTGAAAACCA
 TTCACTAGGAGAGGAGAAACACCAATGGCCACCACAGACAGAGTTGAGTCCCACAGCAAGGGAGAGGCAAGAACGCA
 CAGATATGCAAGTGGATGAGACACTGATCCCCAGGAAAGGTCCAAGTTTATGTTCTGCTCGCTATGGAATAGC
 CCGTGTCTTACATTTCTGCAATTTACACAGGATAGCACAAATGTCTCATGAACATCACCATGGTAGCCATGG
 TCAACAGCACAGGCCCTCAATCCCGCTCAGTGAITCCTCTGAGGTGCTGCTGTGACTCATTTGGTGGCCCTA
 AGTAAAGCCCCAAGAGTCTTCTGCAAGTCCCTCAATACTTGGGGGTGAGTTTGCAATTTGGGAAAGTGGGG
 CCGTCCACAAAGACGAGCAGACTCTGAGCAATTGTTTTATCAGGAATGTTACTGGGATGCTTTACTGCGCATCC
 TCGTAGGTGGCTTCATTTAGTGAAACCCCTGGGGTGGCCCTTTGTCTTCTATATCTTTGGAGGTGTTGGCTGTGTC
 TGCTGCCCTCTCTGGTTFGTTGTGATTTATGATGACCCCTTTTCTATCCATGGATAGCAGCTCAGAAAAAGA
 ATACATCATATCTCTCTTGAAACCAACGGTGGGGTCTCTCAAGCAGCCCTCTTCCATCAAAAGCTATGCTCAGAT
 CTCTACCCATTTGGTCCATATGTTTAGGCTGTTTCAGCCATCAATGGTTTGTAGTACCAATGGTTGTATACATA
 CCACTTACTACTAGCTCTGCTGATGCTTAACATCAGAGACATGGAGTTCTATCTGCCCCCTCTCTTTATGT
 TGCGCTGGGTGATAGGCATGGTGGGAGGCTATCTGGCAGATTTCCCTCTAACCAAAAGTTTAGACTCATCATCTG
 GGCTAATACACAGCAACTGCCCTTGTGAGCTCTCTTGGGGATTAAGCAGATTTGTGTGAGTACAGGAAATTTATAT
 CAATGTCTTAGATATTGCTCCAGGCTATTCCAGTTTTCATGCGGAGCATCAGAGAGATTTTCAGGATATGAC
 CTGTCAITGTACCCACTGTGACGGGATTTCTTCTTAGTCAGGACCCCTGAGTTTGGGTGAGGAAATGCTCTCTTC
 TTGCTGTTTGGCGTTAACCTGTTAGGACTACTCTTCTACCTCATATTTGGGAGAGCAGATGTCAGAGATGGG
 TAAAGAGAGAGAACTCACTCGTTTTCAGAGTTATCCACCTTGGATGGAAAGTCATTAGGCACCGTATTGCAT
 AAAATAGAGGCTTCCGTGATGAAATACCACTGAAAGATTTTCTTCTGCTGGCTCTTTCAATTATGAGA
 TCAGTTCATTATTTTATTCAGACTTTTTTTTGGAGAGATGTAGATGAATAAAATTCBAATAAATGATAAC
 TAAAGAAAAAAGAAAAA

38/162

FIGURE 35

GTGAAACCATTCACCTAGGAGAGGGAACACAAATGGCCACCAAGACAGAGTTGAGTCCACAGCAAGGGAGAG
 CAGAGACGCCACAGATATGCAAGTGGATGAGACACTGATCCCCAGGAAAGTTCCAAAGTTTATGTTCTGCTCGCT
 ATGGAAATAGCCCTGCTCTTACATTTCTGCAATTCACAAACGATAGCACAAAATGTCTCATGACATCACCATG
 GTAGCCCTAGTCAACAGCACAAAGCCCTCAATCCGAGCTCAATGATTOCTCTGAGGTGCTGCTCTTTGACTCATTT
 TGGTGGCCTAAGTAAGGCCCAAGAGATCTTCTACAAAGTCTCTCAATACCTTGGGGGTGAGTTTGCATTTGGG
 AAAAGTGGGGCCCTCCACAGAAACGAAGCAGACTCTGCAGCATTCCTTTATCAGGAATGTTACTGGGATGCTTT
 ACTGCCATCTCATAGGTGGCTTCATTAGTGAACCCCTTGGGTGGCCCTTTGTCTCTATATCTTTGGAGGTGT
 TGGCTGTGTCTGCTGCCCTCTCTGGTTTGTGTGATTTATGATGACCCCGTTTCTATCTCATATGATGACCT
 CAGAAAAGGAATACATCATATCTCTCTTGAACACACAGGTGAGGTCTTCTAAGCAGCCTCTTCCCATCAAGCT
 ATGCTCTCATCTCTTACCCATTTGGTCCATATGTTTGGGCTGTTTCAGCCATCAATGGTTAGTTAGCACATGGT
 TGTATACATACCAACTTACATCAGCTCTGTGTACCATGTTTACATCAGAGACAAATGGACTTCTATCTTGGCCCTT
 CTTTATTTGTTGCCCTGAGCTATAGGCATGCTGGGAGGCTATCTGGCAGATTTCCCTCTAACCAGAAAGTTTAGA
 CTCTACACTGTGAGGAAATTTGCCACAATTTAGGAAGTCTCCCCCTTCAGCACTCATTTGTCTCTGCTCTTA
 CCAATTTCCGGCTATATCAGAGCAACTGCCCTTCTGACGCTCTCTTTCGGATTAAGCACATTTGTCTCAGTCTAG
 GATTTTATATCAATGTCTTAGATATTTGCTCCAGGATTTCCAGTTTCTCATGAGGAGCATCAGAGGATTTTCG
 AGCATAGACCTGTCTATGTATCCCACTGTCTAGCGGATTTCTTCTTAGTCAGAACCTGAGTTTGGTGGAGGAA
 TGTCTCTCTGTTGTCTTTGCCGTTAACCTCTTAGGACTACTCTTCTACCTCATATTTGGAGAGCAGATGTCC
 AAGATGGGCTAAGAGAGAAACTCAGTCTGTTTATGAGTTATCCACCTTGGATGGAAAGTCATTAGGCAC
 CGTATTGCATAAAATAGAGGCTTCCGTGATGAAGATACCAAGTGAAGAGATTTTTTTTCTCTGTGCTCTTTTC
 AATTATCAGATCAGTTCATTTATTTATTCAGACTTTTTTTTGAAGAAATGTAGATGAATAAAATTCATATA
 AATGTATACCTAAGAAAAAAGAAAAA

[illegible]

40/162

FIGURE 37

ATTGCGCCCTTTGCTCCCGGGTGTCCCAGGCCCGGCCGGGTGCGCAGAGCATTGCGGGTGGGGGCCGAGCGCGG
 CGGGCTAGCGGCGCGCGCGGCGCGAGGAGAGGAGAGGCGCGGGGAAGATGCTGGCCGCCAAGAGCGCGGACG
 GCTCGGCGCCCGCGAGCGAGCGGAGGGGCTGACCTTGGAGCGGAGCATTCAAGCTGCTCAACGGCGTGGCCATC
 ATCGTGGGGACATTATCGGCTCGGGGCATCTTCGTGACGCCACCGGGCTGCTCAAGGAAGCGGGCTCGCCGGG
 GCTGGCGCTGGTGGTGTGGGCGCGGTGCGGCGCTCTCTCCATCTGGGCGCGCTCTGCTACCGGGAGCTCGGGCA
 CCACCATCTCCAAATCGGGCGGGACTACGGCTACATGCTGGAGGCTACGGGCTCGCTGCGCGGCTTCTCTCAG
 CTCCTGGATCGAGCTGCTCATCATCCGGCTTTCATCGCAGTACATCTGGGCGCTGGTCTTCCGCCACTACCTGCT
 CAAGCGGCTCTTCCCGACCTGCGCGGTGGCGGAGGGGAGGCCAAGCTCGTGGCTGCTGCTGCTGCTGCTGCTG
 TCACGGCGCTGAACCTGCTACAGCGTGAAGGCGGCCACCGGGTCCAGGATGCTCTTGGCGCGGCCAAGCTCGCTG
 GCGCTCGCGCTGATCATCTGCTGGGCTTCGTCCAGATCGGGAGGGTGAATGTGTCCCAATCTAGATCCCAACTT
 CTCATTTGAAGGCGCCAACTGGATGTGGGGAACATTGTGCTGGCATTATACAGCGGCTCTTTCCTATGGAG
 GATGGAAATACTTGAATTTCTCACAGAGGAATGATCAACCCCTACAGAAACCTTGGCGCTGCGCATCATCATC
 TCCCTGCGCATCTGTGACGCTGGTGTACGCTGTGACCAACCTTGGGCTACTTCACCCCTCTGTCACCGAGCAGAT
 GCTGTGCTCGAGGCGGTGACCGGTGACCTTCGGGAACATATCACTGGGCGCTCATGCTCTGGATCATCCCGCT
 TCGTGGGCTCTGCTGCTTGGGCTCGGCTCGGTCATGGGTCCCTGTTACATCTCCAGGCTCTTCTCTGCTGGGTC
 CGGGAGGGCGACCTGCCCTCCATCTCTCCATGATCCACCCACAGCTCTTCACCCCGGTGGGCTCCCTCGGTGTT
 CAGCTGTGTGATGAGGCTGCTACGCGCTTCTCCAGGACATCTTCTCGGTCTCAACTCTCTCAGCTTCTTCA
 ACTGGCTCTGCGTGGGCTTGGCCATCATCGGATGATCTGGCTGCCCCACAGAAAGCTGAGCTTGAGCGGGCC
 ATCAGGCTGACCTTGGGCTGCTGTGTTCTTCATCTGGGCTGGCTCTTCTCTGATCGGCTCTCTCTTCTGGAA
 GACACCCGTGGGCTGGGCTGCGCTTCACCATCATCTCAGCGGCTCGCCGCTACTACTTCTCGGGGTCTGGT
 GGAAAAACAGCCCAAGTGGCTCTCCAGGGCATCTTCTCCAGACCTCTCTATGTCAGAGGCTCATGCAAGTG
 GTCCCGCGGAGCATAGCCAGGAGGCCGAGGGCG

41/162

FIGURE 38

CCAGGCTCTCCACCCCTACTCCCAATTGAGGAACCCAGGCAGAGGCTCAGGTGTGGCCCAATCACCTG
 ACATCAGAGTTACCTGGGCAGGGCCCACTGAGACCTGGGAGGGGCTACTCGGGACCTGGAGGGCTGGGGGCTG
 CCGGGCCCTTAGGGCTAAGACTCCTACCCCACTGCGCAGAGGGCTCAGAGGCTGGGGGCTGGGCTTCCCT
 TTCAATCGCCCTTTAGAGGCCACCTGTGGGATTGGCCCGGATCTGAAGAGGGCTGTCTCTGTTCCTGATGG
 GCGCTGCGAGCGCCAGCGCTCTCTTTCTGCTGGCCGGCCACTGCCCTCTGCTGTGACGCGCGGACACGAG
 CTACCGGTGGACCCACGCTGCTTCCCTCCCTGGGATCTACACAGACAGGCTTGGCCCTTGGCAACGGCTCGACCCCTG
 TTGGGCTCCTGTGGGACCCCGCCCTCGGACGCTCCTGTTCTGCTCTTCAGCCCTGGATGGGTGCGGCCCTC
 GAGGACCTTGGCTGGAGAGACAGGGCGAGGAGCTGCACCCCTGGACGGAGTCTTGGCCACCCCACTAACATTT
 CCAGCCTCTCCCTCGCCCACTCTTTGGCTTCCGCTGTGCGGAGGTGTCCGGCTTGGACAGGAGCTGTCTGGG
 GAGCTGGCTGTGGCTTGGCACAGAGAAATGTCAAGCTCTCAACAGAGCAGCTGGCTGTCTGGCTCAGCGGCT
 CTCTGAGCCCCCGAGGACCTGGAGGCCCTCCATTGGACCTGCTGCTATTCCTCAACCCAGATGGCTCTCGG
 GGGCCCGGGCTGCAACCCCTTCTTCCCGCATCACAGAGGCTAATGTGGACCTGCTCCGAGGGGGGCTCC
 GAGCGACAGCGGCTGCTGCTCGGGCTCTGGCTGCTGGGGTGTGGGGGGTCTCTGCTGAGCGAGGCTGATGT
 GCGGGCTCTGGGAGGCTTGGCTTGGGACCTGCTGGGGCTTTGTGGCGAGTGGGCGAAGTGTCTGTACCC
 GGCTGTGAGCTGCCCCGGGACCCCTGGACACAGGACAGCAGGAGGCGAGCGGGCGGCTCTGAGGGGCGGGAA
 CCCCCCTACGGCCCCCGCTGACATGGTCTGTCTCCAGATGGACGCTCTCGGGGGCTGTGGCCCTGTCTGG
 CCAGCCCATCATCCGACAGTCCCGCAGGCGATCCGAGGGGCTGTGGCGGCTGTGGCCCTGTCTGG
 GGGGACGCTGAACGAGCACTCTCCGGCCCGGTTCCGGCGGAGTGGAGAGAGACAGCTGTCTTACAGG
 AAGAGGCCCCCGAGTAGACGAGGCTCATCTTCTACAGAAATGGGAGCTGGAGCTGGAGGCTGTCTGGATGCGG
 CCTGCTGGCCACCCAGATGGACCGCTGAACGCCATCCCTTCACTACAGACAGCTGGACGCTCTTAAGCAT
 AACTGGATGAGCTCTACCCACAGGTTACCCGAGTCTGTGATCCAGCACCTGGGCTACCTCTTCTCAGATG
 AGCTCTGAGGACATTGCGAATGGAAATGTGACGCTCCCTGGAGACCTGAAGGCTTTGCTTGAATCAACAGG
 GCACGAAATGAGCTCTCAGGTGGCCACCTGATCGACCGCTTTGTGAAGGAGGGGCGCAGCTAGACAAAGACA
 CCTAGACACCTTGACCGCTCTTACCTGGGTAACCTGTGCTCCTCAGCCCGAGGAGCTGAGCTCCGTCCCC
 CCGAGCAGCATCTGGGGGTGAGGCCCGCAGGACCTGGACACGCTGTGACCCAGGACGCTGGACGCTCTGTATCC
 CAGGCCCCCGCTTCTTCCAGACATGAAAGGCTCGAATACTTCTGTGAAGATCCAGTCTTCTGGGTGGG
 CCCCCACGAGGATTGAAGGGCTGAGTCAAGCAATGTGACGATGGACTTGGCCACGCTCATGAGCTGCGG
 AGGATGCGGTGCTGCGCTTGAATGTGAGTGTGAGTGCAGAAATCTTGGGACCCCGCAGTGGAGGCTTGAAGG
 GGAGAGCGGACCCCGGCTGGGACTGGATCTTACGCGAGCGGACGAGGACCTGGACACGCTGGGCTTGG
 GGCTACAGGGCGGCTTCCCAAGGCTTACCTGGTCTTACAGCTCAGCTTGCAGAGGCTCTCGGGGCGCC
 TGCCTTCTAGGACCTGAGCTTCTTCAACGCTCTGGGCTGCTCTTACCTTCCACCTGGGCTTGGGCGCCCA
 CTCCCTTGTGCGCCCGGCTGCTGGGATCCCGCTGGGCGGAGCAGGCGAGGCTGATCCCGCTTCCAC
 CCGAGAGACTCGGCTCAGTAAACGGGACATGCCCCCTGCAGACGCTAAAAAATAAAAAA

42/162

FIGURE 39

TGGGATCTACACAGACATGAGGCTTGCACAGGGCTCGACCCCTGTGGGGTCTGTGGGAACCCCGCCCTCGGCGAGC
 CTCTCTGTCTCTGCTCTTCAGCCCTGGGATGGGTGCAGCCCTCGAGGACCTCTGGGTGGAGAGACAGGGCAGGAGGC
 TGGCCCCCTGGACCGAGTCTCTGGGCGACCCACCTACATTTCCAGCCCTCTCCCTCGCCAACTCCTTGGCTTCC
 CGTGTGGGGAGGTGTCCGGCTGAGCACGGAGCGGTCCCGGGAGCTGCTGTGGCTTGGCAACAGAGATGTCTC
 AAGCTCTACACAGAGACAGCTGCGGTGCTTGGCTCACCAGGCTCTCTGAGCCCCCGAGGACCTGGGAGCGCCCTCC
 ATTTGGACCTGCTGCTATTCTCTCAACCCAGATGCTCTCTCGGGGCCCGAGGCTGACCCCTTTCTTCTCCCGCA
 TCACAGAGGCCAATGTGGGCTGCTCCCGAGGGGGCTCCCGAGCGACAGCGGGCTGCTGCTCGGGCTCTGGCC
 TGCTGGGGTGTGCGGGGCTCTCTGCTGAGCGAGGCTGATGTGCGGGCTCTGGGAGGCTGCTGCTTGGAGCTGCTC
 TGGGCGCTTTGTGGCGAGTGGGCCGAGTGTCTCTACCCCGGCTGGTGGAGCTGCCCGGGACCCCTGGACATGGTCTGTG
 ACCAGCAGGAGGAGCAGCCAGGGCGGCTCTGACGGGCGGGGACCCCTACGGCCCCCGTGGACATGGTCTGTG
 TCCACGATGGACGCTCTGCGGGGCTGCTGCCGCTGTGGGCGACCCCTATCCGCGACATCCCGAGGGCAT
 CGTGGCGCTGTGGGGGACGCTCTCTCTGGGACCCCTCTGTGGCGGAGCTGAGAGGACCATCTCTCGGGCCG
 GGTTCCCGGGGAAATGAGAGAGACAGCTCTCTCTCAGGCAAGAGGGCCCGAGATAGACGAGAGCTCTATC
 TTCTACAGAGAGTGGGAGCTGAGAGGCTGCTGATGCGGCCCTGCTGCCCCAGATGGACCCGCTGAGAGC
 CATCCCTTTCACCTACAGAGCAGCTGGACCTCTAAAGCATAACTGGATGAGCTCTACCCACAAAGTTACCCG
 AATCTGTGATCCAGCACCTTGGGCTACCTCTCTCTCAAGATGAGUCCCTGAGGACATTCGCAAGTGGAAATGTGAGC
 TCTCTGGAGACCTTGAAGGCTTTGCTTGAAGTCAACAAAGGAGCAAGAAATGAGTCTCTGAGTGGCCACCTGAT
 CGACCGCTTTGTGAAGTGAAGGGGCAAGCTAGACAAAGACACCTAGACACCTTGAACGCTTTTATCCCTGGT
 ACCTGTGCTCCTCAGUCCCGAGGAGCTGAGCTCGCTGCCGCCCAAGAGCATCTGGGGCTCAGGCCCCAGGAC
 CTGGACAGCGTGTGACCCAGGAGCTGGACCTCTCTATCCCAAGGCCCGCTTGTTCAGAGACATGAACGG
 GTCCGATATCTCTGTAAGATCCAGTCCCTCTGCTGGGTGGGGCCCCACGAGGATTTGAAGGCGCTCAGTACAG
 AGAATGTGAGCATGGACTTGGCCAGCTTCAGGAGCTGCGGAGGATGCGGTGCTGCCGTTGACTGTGCTGAG
 GTGCAGAACTTCTGGGACCCACCTGGAGGGCTGAAGGCGGAGGAGCGGACCTGCCCGTGGGGACTGGAT
 CCTACGACAGCGGACGAGGACCTGGACAGCTGGGGCTGGGCTACAGGGGCGCATCCCAAGCGCTACCTGG
 TCTAGACCTCAGCGTGCAAGAGGCCCTCTCGGGAGCGCCCTGCTCTAGGACCTGAGCTGTGCTCACCGTC
 CTGGACCTGCTCTAGCTCTCAACCTGGCTGGCTGGAGGGGCCACTCCCTGCTGGGCCGACCTGCTGGGATCC
 CCGCTTGGCGAGGAGCAGGCGGGTATCCCGTTCCACCCCAAGAGATCT

FIGURE 40

ATACAGCCTGTAAGTGCCTGTGGAAGTGGAGGTGCTCTCCCTCGACCCCTCCOCCCTCCTGTCCCTCTG
 CTCACCCCTCGCTCGTTCCTCCCTCCCTCGGCGAGGGCCGCTTTTATACAACTGCTCAGAGTGGAGGGCGGAT
 AGCTGTCCAGAGTCTCTCCCCACCACTGAGAGGCTCGGCTGCTGCCCCCTCTGCGCGCGGGGAGGACCAAGTT
 CACGGGCCAAGGCTTGGCACTAGGGTCCAGAAATGGCTACCAACAGTCCCTGATGCTTCCGCGAATGGCTGAAAT
 CCAAGTACTACAGACTTTGTGATAAGGCTGAAGCTTGGGGCATCGTCTAGAAACGGTGGCCACAGCCGGGGTT
 GTGACCTCGGTGGCTTCATGCTCACTCTCCGATCCTCGTGTGCAAGGTGCAAGACTCCACAGGCGAAAAAT
 GCTGCCCTACTCAGTTTCTCTTCCCTCGGTGTGTTGGUCATCTTTGGGCTCACTTCGCTTCATCATCGGAC
 TGGACGGGAGCACAGGGCCACACGCTTCTTCTCTTTGGGATCCTCTTTCCATCTGCTTCTCTGCTGCTG
 GCTCATGCTGTGAGTCTGACCAAGCTCTCGGGGGAGGAAGCCCTTTCCCTGTTGGTATCTGGGCTGGG
 CGTGGGCTTCAGCCTAGTCCAGGATTTATGCTATGAMATATGTCCTGACCATGATAGGACCAAGCTCA
 ATGTCCTTTTCTGAGCTTTCCGCTCTCTGCTGGCAATGAGACTTTGCTCTGCTGCTACGCTACGCTCTCTT
 ATGGCGCTGACCTTCTCATGTCTCTCTTCACTCTCTGTGGTCTCTTACGGGCTGGAAGAGCATGGGGCCCA
 CATCTACCTCAGCATGCTCTCTCTCCATTTGCTCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG
 ACCGAGGTGGGATGACACCATCTCACTCGGCTTGGCTGCGCATGGCTGGCTGGTCTGCTGGCTGCTGCTGCT
 AGTCCCGATTTTGGCTGCTCAAGAGCAAGAACCCCATGATTATCTGTTGAGGATGCTTTCTGTAACCC
 TCAACTCTGTAAGAGAGCTATGCTGTGAGAGACAGAGCTACTCTCAAGAGGAAATCACTCAAGGTTTGAAG
 AGACAGGGGACAGCTCTATGCCCCCTATTCCACCATTTTTAGCTGCAAGAACAGGCTCCCCAAGGATTC
 TCCATCCACGGGCCCGAGCTTGGGCGAGCCCTTACAAAGACTATGAAGTAAGAAAGAGGGCAGCTTACTCTG
 TCCCTGAAGAGTGGGACAAATGCGCCGGGCGGAGATCTAGCGGGAGCTCAAAGGATGTGGGCGAATCTTGA
 GCTCTCTGAGAAACTGTACAGGACACTACGGGAACAGTTTGGCTCCCTCCGAGCTCAACCAATCTTCCA
 TGCTGGGCTGCTGTGGGCTAGTAAGACTCCAGTCTTAGAGGCGCTGATGATTTTTTTTTTTTTTTTGTCTCATC
 CTFTGGATACCTTTTAAAGTGGGAGTCTGAGGCAACTCAAGTTTAAAGCTTACTCTTTTTTTTGTGTTTTT
 AAACAGGATCTTGTCTCTGTACCCAGGCTTGAAGTCTGATGCGATCAGAGCCCAATGAGCTTCAAGCTT
 GTGCTCAAGCAATCTCCCTCATCTCCATCTCCCAAGTCTGGGATGACAGGCTGAGGCCAGCTCCAGGCTTA
 GGGCTTAACTCTTGTGTTATTTTCCATGGCTAAAGGTCTGGTCTGCTGAGCTCAAGCTGCTCAACAGCTC
 TGGGGGCTGCTCTCTCACTCACTCACTGAGTGGTCTTGTGAGGCTCTGTGGGCCAGAGAGCTGATATCTGAGC
 AAAAATAGCAAAAGCTCTCTCAGCCCACTGCTGCTGATCTACACTGGAAGCTCACTTGTGAGCCCTGGCTG
 CCCAGCCCTTCTTGTCTGGGTGAGAGAGCTAAAGATCACCTAAATTTATCTCATCTCTAGTGTGCTGCTCAG
 ATTGGGCTCAGCAGCTCCCCAGCAACATTCACAGGCTCACCCCTCTCTTCTTCACTGTCCCAAACTTGTG
 TCAATTCAGAGATCTAATCTCCCTTACGCTCTGCGAGAAATCTTTCAGAGCTCACTGACAGAGCCCGGTG
 CTCTTGTCAAGAGAAATTTGAGMCACTTCTCACTTCAAAATTCCTGGGCTGATCTCTCTCATCTTGCACCT
 CAACCTCTGTAATAGATTTACCGCATTTAGGCTGCTTCTGTAAGTGGGATGCTCTCTAATGGAGAGTG
 TTCAATGTATAAATAGTATTCACTGAGTATGCAATAAGATGTGGTGGCACTCTTCTCATGTTGGTGGCAGC
 AAAAAAAAAA

FIGURE 42

CCCTTGAGACTCAAGATGATTCCTTTTACCCATGTTTCTCTACTATTGCTGCTATTGTTAACCCGTATAAA
 CGCCARCAATCAATATGACAAGATCTTGGCTCATAGTCTGTATCAGGGGTGGGACCCAAAGCCCAATGTCCTGTG
 CCCTTCAACAGATTTTGGGCACCAAAAGAAATACTTCAGCACTTGTAAAGAACTGGGTATAAAAATCCACTGTG
 GGCACAGAAACGACTGTGTATATGAATGTTGCCCTGGTTATATGAGAAATGGGAAGGAATGAAAGGCTGCCACGC
 AGTTTTGCCATTGACCATGTTTATGGCACTCTGGGCTCTGCTGGGAGCCACCAACACGACGGCTATCTGTACG
 CCTCAAACTGAGGGAGGAGATCGAGGGAAAGGGATCCTTCACTTACTTTGCACCGAGTAATGAGGCTTGGGAC
 AACTTGGACTCTGATATCCGTAGAGGTTTGGAGAGCAACGTAATGTGTAAATTAATTAATGCTTTACATAGTCA
 CATGATTAATAAGCAATGTTGACCAAGGACTTAAAAAATGGCAATGATTATCTCTTCAATGATTAACATTTGG
 GGCCTTTTCAATTAACCAATTATCCTAATGGGCTTGTGACTGTTAATTGTGTCTCGAATCATCCATGGGAACGAGATT
 GCAACAAATGGTGTGTGCATGTCTGTGACGCTGTCTTACACAAATTTGGTACCTCAATTCAGAGCTTCATTGA
 AGCAGAAGATGACCTTTTCACTTTTAGAGCAGCTGCCATCACATCGGACATTTGGAGCCCTTGGAGAGAGCG
 GTCACTTCACACTCTTTGGCTCCCAACCAATGAGGCTTTTGGAGAACTTCCACGAGGTGCTCTAGAGAGGATCATG
 GGAGACAAAGTGGCTTCCGAAGCTCTTATGAAGTACACATCTTAATTAATCTCTCAGTGTCTGAGCTATTAT
 GGGAGGAGCAGTCTTTGACAGCTCTGGAAGGAATACAAATGAGATAGGATGTGACGGTGACACTATACAGTAA
 ATGGAAATCAAAATGGTGAACAAAAGGATATTTGTGCAAAATTAATGGTGTATCCATTTGATTGATCAGGTCTTA
 ATTCCTGATTCCTCCAAACAAAGTTATGAGCTGGCTGGAAACAGCAACCACTTCCAGGATCTTGTGGGCA
 ATTAGGCTTGGCATCTGCTCTGAGGGCCAGATGGAGATACACTTTGCTGGCACTGTGATTAATGCATTTCTG
 ATGATACCTCTCAGCTAGGATCAGCGCCTCCTTAATTAATTTCTGAGAAATCACATATTGAAGTAAAGTTGGC
 CTTAATGAGCTCTTACAAACGGGCAATACTCGGAACCACTCGGAGGCAACAGCTCAGAGTCTTGTATATCGTAC
 AGCTGTCTGCTATGAANAATCATGCTGAGAGAAAGGAGTAAGCAAGGAGAAACGCTGCGATTACATATTCC
 GCGAGATCATCAAGCCACGACAGAAATCCCTCCATGAANAATTAAGCAAGATTAAGCGCTTTAGCACTCTCTC
 AGCCTACTTGAAGCTGCAGACTTGAAGAGCTCCTGACACACCTGGAGACTGGACATTTTGTGTCACACCA
 TGAAGCTTTTATGGGAATGACTACTGAGGAAAGGAATTTCTGATCGGGACAAATATGCTCTTCAAAACATCA
 TTCTTTATCACCTGACACAGGAGTTTCTATTGGAAGAGATTGACCTGGTGTACTACATTTTAAAGACC
 ACACAGGAGAACAAATCTTTCTGAAGAGTAAATGATCACTTCTGCTGATGAATGAATGAATGAATGAATGAAT
 TGACATCATGACAAACAAATGGTGTATTTCTGTTGATGATTAATCTCTCTATTCAGCAGACACACCTGTGGAA
 ATGATCACTGCTGGAATFACCTTAATTAATTAATCAATCACTCCAAATTAAGTTTGTGCTGCTGAGCTCTC
 AAGGAATCCCTGCTACTGTCTATAGACCCACACTAACAAAGTCAAAATTAAGAGGTGAGCTGAATTCAGACT
 GATTAAGAGAGGTGAACATAACTGAAGTATCCATGGAGGCCAATTAATTAAGAAATACACCAAAATCATG
 ATGGAGTGGCTCTGGAAATTAATGAAAAGGAGACGAGAGAAACGATCATTTACAGGTCTGAAATTAATTAAT
 CTAGGATTTCTACTGGAGGTGGAGAAACAGAGAACTCTGAGAAATTTTAAAGAAAGTCAACCAAGGT
 CACCAATTTCTATGAGGTTGGTATGCTATTATTTCAAGATGAAGAAATTAAGAGCTGCTCTAGGAGGACA
 CACCGTGGAGGAGTTGCAGCCCAACAAAAGTTCAAGGATCTAGAGAGCAATTAAGGAGAGTCTGCTCAG
 TGAAGGCT

FIGURE 43

CCCTTGAGAGCTCAAGATGATTCCTTTTACCCCATGTTTTCTCTACTATTGCTGCTTATTGTTAACCTATATAA
 CGCCAACAACTCAATTTATGACAAAGATCTTGCGCTCATAGTCGTATCAGGGGTCGGGGCCAAAGGCCAAATGTCCTGTG
 CCCTTCACACAGATTTTGGGCACCAAAAAGAAATACCTTCAGGACTTTGTAAAGAACTGGTATAAAAGTCCATCTGT
 GGCACAGAAAAGCACTGTGTTATATGAATGTTGCCCTGGTTRATGAGAAATGGAAGGAATGAAAGGCTGCCACG
 AGTTTTGCCCATTCAGCACTGTTTATGGCACTCTGGGCACTCGTGGGAGCCACCCACAAAGCAGCGCTATTCTCGACG
 CCTCAAAACTGAGGGAGGAGATCGAGGGAAAGGGATCCTTCACCTTACTTTGCAACCGAGTAATGAGGCTTGGGAC
 NACTTGGATTCGTGATATCCGTAGAGGTTTGGAGAGCAACGTGATGTTGAATTACTGAAATGCTTTACATAGTCA
 CATGATTATAACAGAAATGTTGACCACAGCACTTAAABAAATGGCATGATTTATTCCTTCAATGTATACAAATTTGG
 GGCTTTTCATTACCATTTATCCTAATGGGTTGTCACTGTTAATTTGTGCTCGAATCATTCATGGAAACCAAGATT
 GCACAAATGGTGTGTGTCATGTCATTGACCGTGTGCTTACACAAATTTGGTACCTCAATTCAGACTTCATTGA
 AGCAGAGAGATGACCTTTCATCTTTTGAAGCAGCTGCCATCACAATCGGACATATTGGAGGCGCTTGGAAAGAGAG
 GTCACTTCACACTCTTTGCTCCACCAATGAGGCTTTTGAAGAACTTCCACGAGGTGCTCTAGAAAGGATCATG
 GGAACAAATGGCTTCCGAAGCTCTTATGAAGTACCACTCTTAATACCTCTCCAGTGTCTCGAGCTATATAT
 GGGAGGAGCGCTCTTGAAGCAGCTGGAAAGGAATACAAATGAGATAGGATGTGACCGTGACAGTATACAGTAA
 ATGGAAATCAAAATGGTGAACAAAAGGATATTGTGACAAATATGSGTGTGATCCATTTGATTTGATCAGGTCTTA
 AGCTGTCTGCAATGGAATTCATGCAATGAGAGAGGGAGTAAGCAAGGGAGAAACGGTGGCAATTCACATATTC
 GCGAGATCATCAGCCAGCAGAGAAATCCCTCCRTGAAGAAAGTAAACCAAGATTAAGCGCTTTAGACCTTCCCTC
 AGCCTACTTTGAAGCTGCAGACTTGAAGAGCTCCTGACACACCTGGGACCTGGACATTTATTTGTGCCACCA
 TGATGCTPTTGAAGGAATGACTAGTGAAGAAAGAGAAATTCGATACGGGACAAATATGCTTTCAAACATCA
 TTCTTTATCACCCTGACACCGAGGATTTTCATTGGAAAAGGATTTGAACCTGGTGTACTAACATTTTAAAGACC
 ACACAGGGAAGCAAAATCTTTCTGAAGAGTAATGATACACTTCGGTGAATGAATGAAATGAAATCAAGAAATC
 TGACATCATGACACAAATGGTGAATTCATGTTGTAGATAAACTCCTCTATCCAGCAGACACACCTGTTGAA
 ATGATCAACTGCTGGAATACTTAATAAATTAATCAAAATACATCCAAATTAAGTTTGTGCTGGTAGCACTTC
 AAAGAAATCCCGTGACTGTCTATAAGCCATTTATTAATAAATACACCAAAATCATTGATGAGACTGCCCTGGGA
 AATACTGAAAAGAGACACGAGAGAGACGAATCTTACAGGCTCGGAATAAATACACTAGGATTTCTACTG
 GAGGTGGAGAAACAGAGAAATCTGAAGAAATGTTTACAGAGAGACACACCCCTGAGGAAGTTGCAAGCCAC
 AAAAAGTTTCAGGATGTAGAGACGATTAAGGAGGTCCTTCTCAGTGAAGGCG

FIGURE 44

CCCTTGAGACTCAAGATGATTCCCTTTTACCCATGTTTTCTCTACTATTGCTGCTTAATGTTABCCCTATAAA
 CGCCAAACRATCATTATGACRAGATCTTGGCTCATAGTCGTATCAGGGGTCGGGACCAAGGCCCAAAATGTCGTG
 CCCTTCACACAGTTTTTGGGCACCAAAAAGAAATCTTCAGCCTTGTAAGAACGCGGTATAAANAAGTCCATCTGT
 GGACAGAAACAGCACTGTGTTATATGATGTTGCCCTGGTTATATGAGRATGGAGGAAATGAAGGCTGCCACG
 AGTTTTGCCATTGAACATGTTTATGGCACTCTGGGCATCTGGGAGCCACCTACAAACGACGCGCTATCTGACG
 CCTCAAAATCTGAGGAGGAGATCGAGGGGAAGGATCCTTCACTTACTTTGCCACCGAGTAATGAGGCTTGGAGC
 AACTTGGATTCTGATATCCGTAGAGGTTTGGAGACCAACGTGAATGTTGAATTAAGTGAATGCTTTACATAGTCA
 CATGATTAATAGAGAAATGTTGACCAAGGACTTAAAAAATGGCATGATTATCTCCTTCATGTATACAAATTGG
 GGCTTTTCATTAACCATATATCCATAATGGGTTGTCACTGTTAATTTGTCTCGAATCATCCATGGGACCCAGATT
 GCAACAAATGCTGTTGTCCATGTCACTTGAACCTGTGTCTTACACAAATPGGTACCTCAATTCAGAGCTTCATTGA
 AGCAGAAAGTGAACCTTTCATCTTTTAGAGCAGCTGCCATCAGCTCGGACATATTGGAGGCGCTTGGAGAGAGCG
 GTCACTTCACACTCTTTGCTCCCACTAGAGGCTTTGAGAAACCTTCCAGAGGTGTCTCAGAAAGGATCATG
 GGAGACAAAGTGGCTTCCGAGCTCTTATGAGGTACACACATCTTAATACTCTCCAGTGTCTGAGCTATATTAT
 GGGAGGAGCAGCTCTTTGAGACGCTGGAGAGAAATACATTTGAGATAGGATGTGACGCTGACAGTATAACAGTAA
 ATGGAATCAAAATGGTGAACAAAAGGATATTGTGACAAATTAATGGTGATCCATTTGATTTGATCAGGTCCATC
 ATTCCGTGATTTGCCAAACAGTTATTGAGCTGGCTGGAAACACAGCAAAACACCTTCACGGATCTTGGGCCCA
 ATTAGGCTTGGCATCTGCTCTGAGGCCAGATGGAGATACACTTTGCTGGCACCTGTGCAATTAATGCATTTCTG
 ATGATACCTCTCAGCATGGATCAGCGCCTCCTTAAATTAATTTCTGCAGATCACATATTGAAAGTAAAGTGGG
 CTTAATGAGCTTTACACAGGCAAAATCTGGAACCCATCGGAGGCCAAACAGCTCAGAGTCTTCGTATATTCATC
 AGCTGTCTGCATTTGAATTCATGCTGGAGAAAGGAGTAAGCAAGGGAGAAACGGTGGGATTCACATATTCTC
 GCGAGATCATCAAGCCAGCAGAGAAATCCCTCCATGAAAGTTAAACACAGATAAGCGCTTTAGCCCTTCTCTC
 AGCTTCTTGAAGCTTGAAAGAGCTGAAAGAGCTCCTGACACAACTGGAGACTGGACATTATTGTGSCCAACCA
 TGATGCTTTTGAAGGATGACTAGTGAAGRAAAGAAATCTGATACGGGACAAAATGCTCTTCAAAACATCA
 TTCTTTATCACTGACACAGGAGTTTCAATTTGAAAGGATTTGAACCTGGTGTACTAATTTTAAAGACC
 ACACAGGAGCAGAAATCTTTCTGAAGAGATTAATGATACACTCTGTTGAATGAATTTGAATCAAAAGAACTG
 TGACATCATGACACAAATGGTGAATTCATGTTGTAGATAAACTCCTCTATCCAGCAGACACACCTGTGGAA
 ATGATCAACTGCTGGAAATCTTTAATAAATTAATCAATACATCCAAATTAAGTTTGTTCGGGTAGCACCTTC
 AAAGAAATCCCCGTGACTGTCTATAGACCCACACTAACAAAGCTCAAAATTTGAAGGTGAACCTGAATTCAGACT
 GATTAAAGAGGTGAACAACTACTGAAGTATCCATGGAGAGCCAAATATTAAAAATACACCAAAATCATTTG
 ATGGAGTGCTGTGGAAATTAACCTGAAGAGAGACCGAGAGAACGAATCATACAGGTCTGAAATTAATAC
 ACTAGGATTTCTCTGAGGCTGGAGAAACAGAACTCTGAGAAATTTGTTACAGAGAGACACACCCGTGAG
 GAGTTGCAAGCCAAACAAAGGTTCAAGGATCTGAGAGACGATTAGGGGAGGTCGTTCTCAGTGAAGGGC

48/162

FIGURE 45

CCCTTGAGACTCAAGATGATTCCTCCCTTTTACCCATGTTTCTCTACTATTCCTGCTTATTGTTAACCCATATAAA
 CGCCACACATCATTTTGTACAGATCTTGCTCATAGTCGTATCAGGSGTCGGGACCAAGGCCCAAAATGCTCTGTG
 CCCTTCAACAGATTTTGGGACCAAAAGAAATACTTCAGCACTTGTAAAGACTGGTATAAAAGTCCATCTGT
 GGAACGAAACCGACTGTGTATATGAATGTTGCCCTGGTTATATGAGAAATGGAAGCAATGAAGGCTGCCCCAGC
 AGTTTTGCCCAATGACCATGTTTATGCACTCTGGGCATCTGGGAGCCACCACAGCCAGCGCTATTCTGAGC
 CCTCAAACTGAGGGAGGAGATCGAGGGAAGGGAATCCTTCACTTACTTTGACACCGAATANTGAGCGTTGGGAG
 AACTTGGATTCGTATATCCGTAGAGCTTTGGAGAGCAACGTGAATGTTGAATTACTGAATGCTTTACATAGTCA
 CATGATTAAATAGAGATATTTGACCAAGGACTTAAAAAATGGCATGATTATTCCTTCAATGTATAACAAATTTGG
 GGCTTTTCATTAACCATATCTCTAATGGGGTGTCACTGTTAATTGTGCTCGAATCATCCCTGGGAACCAAGATT
 GCAACAAATGGTGTGTCTCATGTCTTGAACCGTGTCTTACACAAATTTGTAACCTCAATTCAGACTTCATTGA
 AGCAGAGATGACCTTTTCATCTTTTAGAGCAGCTGCCATCAGATCGGACATTTTGGAGGCCCTTGGAGAGAGCG
 GTCACTTCACTCTCTTCTCCCAACATGAGGCTTTTGAGAACTTCCAGAGGTGTCTTAGAAAGGATCATG
 GAGACAAAGTGGCTTCGAGAGCTTTATGAAGTACCCATCTTAAATACTCTCCAGTGTCTGAGCTCTATTAT
 GGGAGAGCAGCTCTTTCAGACGCTGGAAGGAATACAATTGAGATAGGATGTGACGCTGACAGTATAACAGTAA
 ATGGAATCAAAATGCTGACCAAAAGGATATTTGTGACAAATATGCTGTATCCATTTGATGATCAGGCTCTTA
 ATTCTCGATTCTGCCAAACAGATTATTGAGCTGGCTGGAAACAGCAAAACCACTTCACGGATCTGTGGCCCA
 AATAGGCTTGGCTCTGCTCTGAGGCCAGATGGAGATACACTTTGCTGGCACCTGTGAATANTGATTTTCTG
 ATGATACTCTCAGCATGGATCAGCGCCCTCTTAAATTAATCTGCGAATCATCATTTGAAGTAAAAGTTGGC
 CTTAAATGAGCTTTACAAACGGGCAATATCGGAACCCATCGGAGGCCAAGCAGCTCAGAGTCTTGTATATCTGAC
 AGCTGTCTGCATTTGAAATTCATGCAATGGAGAAAGGGAGTAAAGCAAGGGAACCGTGCATTCACATTTCC
 GCGAGATCATCAGGCCAGCAGAGAAATCCCTCCATGAAAGTTAAACCAAGATAAGCGCTTTAGCACCTTCCXC
 AGCCTACTTGAAGCTGCAGACTTGAAGAGCTCCTGACACACCTGGAGACTGGACATTATTGTGCCCACCA
 TGATGCTTTTAAAGGAATGACTAGTGAAGAAAGGAATCTGATACGGGACAAAAATGCTCTTCAAAAGATCA
 TTCTTTATCAGCTGACACAGGAGTTTTTCATTGAAAAGGATTTGAACCTGGTGTACTTACATTTTAAAGACC
 ACACAGGAGAGCAATCTTTCTGAAGAGATTAATGATACACTTCTGCTGAATGAATGAATGAATCAAGAAATC
 TGACATCATGACAAACAAAGGCTTAATTCATGTTGTAGATTAACCTCCTCTATCCAGCAGACACACCTGTTGGA
 ATGATCACTGCTGGAATACTTAAATAATTAATCAATATCATCCAAATTAAGTTGTTCTGCTGATGACCTCTC
 AAGAAATCCCCGTGACTGTCTATTAAGCCATTTATAAAAATACACCAAAACCTTATGATGAGATGCTCTGGA
 AATAACTGAAAAGAGACAGGAGAGACGAATCATACAGGTCCTGAAATTAATATACCTAGGATTTCTACTG
 GAGGTGGAGGAACAGAGAAATCTGAGAAATTTGTTACAAGAGAGGTCACCAAGGTCAACAAATTCATTGAA
 GGTGCTGATGCTCTTTATTTTGAAGATGAAGAAATTAAGAGCTGCTTCAGGAGAGCACACCGCTGAGGAGGT
 GCAACCCACAAAAATTCAGGATCTAGAGACGATTAAGGGAAGGTCTTCTAGTGAAGGCC

49/162

FIGURE 46

ACACGGAGCCAGGAGTCTAACACGTGCCGAGTCG99999CTCGCACGAAGCCGCCGTGGCCGCAATGAAGGTGA
AGGCCGCCGCCGTCCGCCGCCGAGGTGGGATCCCGAGGCCCTCTCCAGTCCGCCGAGGGCCACCACCGGCCGT
CTGCCGCCGCCGCCGCCGAGGTGGGACACGGCCGACGTGTTAGGACCCGAAAGCAGGTGAACATATGCTCG99
CAGGGCCGAGCCAGAGGGAACCTCTGGTGGAGTCCGCTAGCGGTCCTGACGTGCAAACTGGTCTGTCGACCTGG99
TATAGGGGCCGGGCTCCGCGCGAGGCCGCTCGACGCTCCTGAAACCTTGGCGCGCGCTGGGCCACTGGGCCCGG
AGCGATGAAGATGGTCGCGCCCTGGACCGGGTCTACTCCACAGCTGCTGCTTGTGCTGCCATGTCCGCCACCG
GCACCATCTGCTGTCGGCGCTCTGGTATCTGATCATCATGCTGTGTGACTGTTGATTTTGTGAGTGGCTGGCT
GATCCGGATCAGTATAACTTTCAAGTTCGAACTGGGAGGTGACTTTGATTTGATGGATGATGCCAACATGTG
CATTGCCATTTGCCGATTTCTCTTCTCATGATCCTGATATGTGCTATGGCTACTTACGGGCGCTACAGCAACCGG
CAGCCCTGGATCATCCCATTTCTCTGTTACCAATCTTTGACTTTGCCCTGAACATGTTGGTTGCAATCACTGTG
CTTATTTATCCAACTCCCAATCAGGAATACATACGGCACTGCTCTCTAAATTTCCCTACAGAGATGATGTGAT
GTGATGAATCTACCTGTTTGGTCTTATTAATCTCTCTGTTTATTAGCATTTATCTTGACTTTTAAGGGTTACT
TGATTAGCTGTGTTTGGAACTGCTACCGATACATCAATGCTAGGAACCTCCCTGATGTCCTGGTTATGTTACG
AGCAATGACACTACGGTCTGCTCTACCCCGTATGATGATGCCACTGTGAATGGTGTGTCGCAAGAGGCCACCGCC
ACCTTACGTGTCTGCCCTTACGCTTCAAGTGGGGCGAGCTGAGGGCAGCGCTGACCTTGCAGACATCTGAGCA
ATAGTCTGATTTATTTCACTTTTGCCATGAGCCCTCTCTGAGCTTGTGTTGCTGCAATGCTACTTTTAAATTT
TGAATGTTAGATTTGAAACTCTAGTTTTCACCATATGCTTTGCTAGAACCTGTGATAGATTAAGTGTAGAAAT
CTTCTGTACGATTTGGGGATATAATGGGCTTCACTAACCTTCCCTAGGCATTTGAAACTTCCCCCAATCTGATG
GACCTAGAACTCTGCTTTTGTACCTGCTGGGCCCAAGTTTGGGCAATTTTCTCTCTGTTCCCTCTCTTTTGAA
AATGTAAATTAACCAAAATAGACAACTTTTCTTCAGCCATTCCAGCATAGACAAACCTTATGGAA
CAGGATGTCAATTTGTAAATCAITTTCTAATTAGGTAATAGAACTCCTTATGTATGTGTACAAAGATTTT
CCCCAACAATCCCTTATGACTGAAGTTCAATGACAGTTTGTGTTGGGTGGTAAGGATTTTCTCCATGGCT
GAATTAAGACATTAGAAAGCACCGGCCGTGGGAGCAGTGAACATCTGCTGACTGTTCTGTGGATCTTGTGT
CCAGGGACATGGGGTGAATGCTCTGATGTGTAGAGGGTGAATGGATGTGTTTGGCGCTGCATGGGATCTG
GTGCCCTCTTCTCTGGAATCACATCCACCCAGGGCCGCTTTACTAAGTGTTCGCCCTAGATTTGGTTC
AAGAGGCTATCCCACTGACCTTTATCAATGGAAATGGGATATATTTGATATACTTCTGCCATACATATGAA
AAGGGTTTCTTTTCCCTGCAAGCTACATCCTACTGCTTTGAACTTCCAGATATGCTATGTCACCTTTTAAAT
GTAAACTTTTCAAAAAATAGAGGTTCCTTCTGTATGCGCTTTTACCTTGACTACCTGATTTGCAAGGG
ATTTTATATATTATATGTTACAAAGTCAGCAACTCTCCTCTGSGTTTATTATGAATGTGCTGTAATTTAG
TSTTTGCCAATTAACAGAGTTTGGCCCAAAAAAAA

50/162

FIGURE 47

ATTCGCCCTTCGGAAAGATGGTGAACCTATGGCTGGGCAGGGCGGGCTCCAGGGCGAGGGGGTCGACGCTCCTGAA
AACTTGGCGCGCGCGCTCGCGGCCACTGGCGCCCGGAGCGATGGAAGATGGTCGGGCCCTGGACTCGGTTCTACTCCA
ACAGCTGCTGCTTGTGCTGGCAATGTCCGACCGGGCAACATCCTGCTCGGGCGCTCGGTATCTGATCATCATGCT
GTGGTACIGTTGATTTTATTGAGTGGCCTGGCTGATCCGATCAGTATTAACCTTTTCAAGTTCGTAACCTGGGAGG
TGACTTTGAGTTTCATGGATGATGCCAACATGTGCATTGCCCATGGCGAATTCCTTCTCATGATCCTGATATGTG
CTAGGGCTACTTACGGAGCGTACAGGCAACGGCGAGCCTGGATCATCCCATTTCTCTCTTACCGATCCTTTGAC
TTTGCCCTGAACATGTTGGTTGCATTCACCTGTGCTTATTTATCCAACTCCATTCAGGAATACATACGGCAACT
GGCTCCTAATTTTCCCTACAGAGATGAGGTCTATGTCAGTGAATCCTACCTGTTTGGTCTTATATTTCTCTGT
TTATTAGCATTAECTTGACTTTTAAGGGTTACTTGATTAGCTGTGTTTGGAACTGCTACCGATACATCATGGT
AGGAACCTCCTCTGATGTCCTGGTTTATGTTACCGCAATGACACTACGGTGTCTGCTACCCCCATATGATGATGC
CACTGIGATGGTGTGCTGCCAAGGAGCCACGGCCACCTTACGCTGTCTGCCTAAGCCTTCAGTGGGCGGAGCTGA
GGGCAGCAGCTTGACTTTGCAAGCATCTGACAGAGGGC

51/162

FIGURE 48

AGCGCCATGCGGGCGAGCCGGGGGCGGGGGCCCGGGCCGGGGGCCCGGCCACTGCTGCTGTTCTTGGGGGCGCG
 GCTGGTCTCTGGGCTCTGGGGGCGCTGCCGCGCGCTGAGGGCGGGCAGCGCGGTTGAGGGCCGAAGAGCTGGTGAAGG
 GAGAGCCGGCGGTGGGAGCGCTGCCAAGCAGACGCGGGGAAGAGCCGGGCCACAGCGGCTGGGGAGGATGAG
 GCGTCTGTGGACGGCGCCCGTGGCGAGCTGGCGGGGCCAAGAGGTGCTGCAAGAGCTCGCTGCGGTGACCGG
 CACCGGCTGGCTGGAGCTGACAGCCAGGCTGGGAGGAGTGAACCGAGAGGGCGGSCAGCGGCGATGCCAGS
 CCGTTCAGCTACGCTCCAGGCTCCCCACAGGTCTCTGGGCACTCAATCATGCCCTGCCATTCTGAGGCT
 ACAGAGGCGAGCGGGCCACCTCCCCACUCCGGCGACAGCTGAGGCCAGCTTCGAACTCCCAAGGAGAG
 CCGCTTGAGGTTTGGCTGAACTCGGGGGCAGTACACCCGACCTCAAGTGGCAGAGCTGACTTACCCATTTC
 AGGGCACCTTGGAGCCCGACCGGCATCAGATATCTTGRCATCGACTACTTCGAAGGACTGGATGGTGGGGT
 CGTGGCGCAGATCTGGGGAGCTTCCCGAGGTCAACAGGACCTCAGAGAACCCCTGATACTGAGGGAGAGC
 CCGTTCCTGGAGCCTGCTTGGCTTATACGATGATTTACCCCTTCGATGAATCTGATTTCTACCCCGACCAT
 CCTTTTATGATGACTTGCATGAGAGGAGGAGGAGAGGAGGATGACAAAGATGCACTAGGAGGTGGAGACCTA
 GAAGATGAAATGAGCTTCTAGTGCCCACTGGGAGGCTGGTCTGGGGCCCGGGACAGGCGAGCCACAGTCTG
 GTGGCATGCTGCTCCCTCCACAGCAGACTCTGGGGTGGTCCCGGAGCAGCATCGCCCTCAGGCCCCCGCCAG
 GAGAGCCAGGCGAGGACTTGGCTCCAGTGAAGATGGCACTGAGTGGCGAGTGGCTTTCTGCGGCTAACGGC
 TCGTCCGGTCACTGTGCGACCTCTTCCAGTTACTGTCAATGGCGGCGAGTCTACTGGTGGAGAACAT
 AGGGGCCCTCTGCAAGTGCACAGCGCAGACTACATCTGGCAGAGGGGATGCGCTGCGAGTCCATCATCACCG
 ACTTCCAGGTGATGTGCTGAGCGTGGGCTCGGCTGCCCTCGTCTGCTCCTGCTCTTCATGATGACGGTGTTC
 TTTCCAGAGAGCTCTACTGCTCAAGCGGAGAAATACCAAGTGGCTGGAGCCAGCAATTCGGAGCCCATC
 TGGCTCCAGAGTAACTTCTCCCTCTCCAGCTTGGGAGGCTCTCACCCAAATGATGATCTTGTGCTC
 CCCCAAAATCCAGGAGGTTCTCAAGTCTGCTGAAGAGGAGGATCATTTAAGTCCAGAACTTAACTTAAAG
 CAGAGCAGAGAGAGGAGGAGCGGGGTAGTGGTGGGGTAGGGAGAGAACATATCTCCTCTGTGACAGAGTCT
 ATTCTGTGAACATTGTTAAGTC

FIGURE 50

CTCGCTCCAGGGGAGAGAGAGAGGGGCTCTGACAGGGGGGACAGAGACCGCAGCTACCTGCCGGGTGCGCCGCCAC
 CCAGAGAGCGCTCGCTTCGCCCCCTTTCTCTCCCCCGCCGCCACCTCCTTATTGCTGCTAGTTTGGACGCGCCAG
 CTCCTGCSCCTTCGCTTCGCGTTTGAATCTGGGCTCGCCCTTCGTATTATGCTCTGCACCTCGAAGAGGAATTTGG
 GGAGGATTATCAGGTAGTGAACACATCTGCCAGCGGCTCGGGCTTCGAGCCCGCAGGGGGCCAGGCCAGGACCTC
 AGCAGCAGCTTTGTGCCAAGAGAGAGCGGACAGCGGTTCTGGACAGAGAGCGCCGCTGCAATGTACAGCAGCGG
 AACCTGGGCAGCGAGAGACAGCGCGCTACCTCTCGGACCTCTTCAACAGCTGTGTGGACCTCAAGTGGCGCTGGA
 CCTCTTCATCTTCATTCTCACTACACCGTGGCTTGGCTTTTCATGGCGTCCATGTGGTGGGTGGGTGATCGGCTACA
 CTCGGGGCGACCTGAACAAAGGCCACGTCGGTAACACACGCGCTTCGCTGGCCAAATGTCTATAACTTCCCTTCT
 GCTTTCCTTCTTCATCGAGAGCGGAGGCCACCATCGGCTATGGCTACCGATACATCACAGACAAGTGCCTCCGA
 GGGCATCATCTCTCTCTTCCTTCAGTCCATCTCTGGGCTCCATCGTGGAGCGCTTCCTCTATCGGCTGCATGTTCA
 TCAAGATGTCCAGGCCAAGAGAGCGCGCCGAGACCTCATGTCTCAGCGAGACCGGCTGATCTCCATGAGGGAG
 GGAAGACTCACGCTTATGTTCCGGTGGGCAACCTCGCGACAGGCCACATGGTCTCCGGCGAGATTCGCTGCAG
 GCTGCTCAATCTCGCGACACACCTGAGGGTGAATTCCTTCCCTTCGACCACTTGAATCTGGTGTAGGTTTAA
 GTACAGGGCCAGATCAACTTTTTCTGTGTCCCCCTCACAATTTGCCACGTGATCGATGCCAAGCCCTTT
 TATGACCTATCCCAAGCGAGCATGCAAACTGAGACCTTCAGATTTGCTGCTATCTAGAGGCAATGTGGAGAA
 AACTGGGATGACTTGTCAAGCTCGAACATCATATACTGAGATGAAGTTCTTTGGGGTCATCGTTTTTTCTCG
 TAAATTTCTTAGAGAGGGATTCCTTAAAGTTCATCTACTCCAGTTCCGCGCAACATTTGAATGCCACCCCA
 CCTTACAGTGTGAAGAGAGCGAGGAGGAATGCTTCTCATGTGCTGCCCTTAAATAGCACACGCCATAACTAACAG
 CAAAGAAAGACATATCTCTGTGAATGCTTAGATGGATAGATGATATTACTACAAACTACCATCTAGCTGC
 AGAAATATCTCGAAGAGAGACCTTCCCAAAAACCTCTTGAGGATGAGTTCTACAACTTCAGAAAAGCCCTAC
 AGCTTGGGAGACTGCCCATGAAACTTCAAGCAATAAGTTCAGTTCCGGGCAACTCAGAGAGAAACTGGTATC
 TAAACCCACCAAGATGTTATCTGATCCCATGAGCCAGTCTGTGGCTGATTTGCCACCAAGACCTTCAAAAGATGG
 CTGGAGGAGCAGCTAGAGTGAAGGGAACTTCCAGCCAAATTAAGAGAAATGAATCTGATCGCTTCACATTA
 CAAGCACTCCCTTAGGCATTTATTTAATGTTTGAATTAAGTAAATAGTCCATATTTGGCGATGAGGTAACTCC
 CTAAGGAATCTGAAGTATATTTTTCTCCGCTCTACAGCAATTTGAGAGACCTCTCTCTTCCCAATATTG
 CGAATGTGCAGAAAGCAACAGTTACGGAGGGAGGACATCATAGGAAGTTATTAACGGGCATGATTTATCAGAT
 CAAGCATGCANTATGTGCARATTTTGCAATTTAGTTTTATGGCATGATTTATATGGCATTTTATATTTGAT
 ATTCTGAAAAAATAATATATATATATTTTAAGGGGAGATACTCTCCCTGACATTTCTAACATATGATTTAA
 GCCAATCATGAGTGAATAGCTTTCCAGGGCGATAAATCAATATATGCTCTGTGTGTGTGTATGATATAC
 ACATATACATATATATATACATACATACATACATACATACATACATATATATATATATATATATATATAT
 TTTGTTCAAGTGTGATGCTCTTGTCATGTTTACTTTATTAAGATAGGAGGCTACTGGCATTAATTTATTA
 CCMAATTTTTAGCCTTAATTTTTGTCAATTTAAATCTGATTTAATCTTTCTGCTGTTTAAGGCTCTGGGA
 GGCCTTCAATGTTATTTATATAGAGAAATCACACAAGTTTGTGCTATCTATGGCCCTGCAAAATATAACCAT
 TACATGTTTAAATTTGTAATTTTATAGCATCCAGTACTCAGTATAGCATGACATTTCTATGATTTTTTAA
 ACTTCTGCTAGTACTGGGAGAAATATTTGTTGATTAATTTAGAAATTTTCTTCTTCTAGACTATTTAAATCTG
 CAATCTGCTTTTGTATATGATCTAATACAAAGATGAGCTCTGAACAACCACTGATCATGTTTATAGACATG
 CCAAGTTATATGAAATATATCAGATCTGTGTGAAGTTACACAATTAATTTGCTGCTTTCAAACTGAGTAAAT
 TGGAAACATTTTCTTCTTTCTGGAAATTTTGTCCCTTTAAAAACCAATCATTTTAAAGAGCATGCAAT
 GCAATGAACAGATGAATATTTATGCTTAAATAAAAAABAAAAA

FIGURE 51

GAGAGGGCTCCTTCAGGGCTTCGCTT**ATG**CCCTTCTTCAGAGACACAGCTGTCAAGCTCTCTTACTCTGTTGTCAG
 ACTGTCCTTCTCTAGGCTTACAGAGATGGGGCAGCCACCTACAGTGGATGCTGCTCTGCACCTCATCTGCTGAGCC
 CCAAAAGCCTTCGAGCTGGAAGAGAGGCGGCTGTACTGGAAATGTAGGACAGCTGACCCACGGGATCATCTGAGCTG
 GGGCCCTACACCTTCGAGCAGGACAGCTCTCTATGTCAATGGTTTCAOCCATCAGAGCTCTATGAGCACTACAGAG
 AACTCCTGATACCTCCACATGCACTTGGCAACCTCGAGAACTCCAGGCTCCCTCTGTCTGGAOCTACGACCGGCCA
 GGCTCTCTCTGGTGGCTATTACAAATTNACTTCAOCCATCACTAACCTGGGGTATGAGGAGAACATGCACTACCCCT
 GGCTCTAGAAAGTTTAAACACCAACGAGAGAGCTCCTTCAGGGCTCTGCTCAGGGCTCTGTTCAAGAACACCTAGTGT
 TGGCCCTCTGTACTCTGGCTGCAGACTGACCTTGTCTAGGGCCAGAGAGGATGGGGCAGCCACCCAAAGTGGATG
 CCACTCTGCACCTTACCGCCCTGATCCCAAAAGCCTTGGACTGGACAGAGAGCAGCTATGCTGGGAGCTGGAGCCAG
 CTAACCCACAGCACTCACTGAGCTTGGGCCCTTACACCTTGGACAGGGACAGTCTCTATGTCAATGGTTTCAACA
 CGGGAGCTCTGTGGCCCACTAGCATTCCTGGGACCCCAAGCTGGACCTGGGAACCTCTGGGACCTCCAGTFTT
 CTAACACTGGTCCCTCGGCTTGGCAGCCCTCTCTGGTGGTCTATTCACTCTCAACTTCACCATCACCAACTGGCG
 TATGAGGAGAACATGACAGCCTCTGGCTCCAGGAATTTAAACACCAACGAGAGGGTCTCTCAGGGCTCTGCTCAG
 GTCCCTCTTTCAGAGAGCACTAGTGTGGGCCCTCTGTACTCTGGCTGCAGACTGACTTTGGCTCAGGGCTGAAAGGG
 ATGGGACAGCCACTGGAGTGGATGCCATCTGCACCCACCACTCTGACCCCAAAAGCCTTAGGCTGGACAGAGAG
 CAGCTGTATTGGGAGCTGAGCCAGCTGACCCACAAATATCACTGAGCTGGGCCACTATGCTCCCTGGACACAGCAG
 CCTCTTTTCTCAATGGTTTCACTCACTGAGAGCTCTGTGTCCACCACTAGCACTCTCTGGGACCCCAAGCTGGATC
 TGGGAGATCTAGACTTTCAGCTCTCGATATTFTTGGGCCCTTCAGCTGCCAGCCATCTCTGCTGATCATATTACCTC
 NACTTCAACCTCACTTACCTTGGCTTGGGTTTGAAGAGAACATGTGGCTTGGCTCCAGGAGTCTTCACTCTACAGAGAG
 GGTCTCTTCAGGGCTGTCTAAGGCCCTTGTTCAGAGAACACAGTGTGGCCCTCTGTACTCTGGCTCCAGGGCTGA
 CCTTCTCTCAGGCCACAGAAAGATGGGAAGCCACCGAGTGGATGCCATCTGCACCCACCTCTGCTGGCCCTCACA
 GGCCCTGGGTTGACAGAGAGCACTGTATTGGAGCTGAGCCAGCTGACCCACAGCACTCTGAGCTGGGCCCT
 TACACACTGGACAGGAGACAGCTCTCTATGTCAATGGTTTCAOCCATCGAGCTCTGTGACCCACCCACCAAGCAG
 GGCTGGTACAGCAGGAGCCATCTCACTCTGAATTCACCATCAACCAOCTGGCTCATGGCCAGCATGGGCCATGGGCCA
 CCGGGCTCTCTCAGGTTCAACATTCACAGAACAGCTCATGAGACACCTGGCTCAGTCTTGTTCAGAGAGGACAG
 CAGCACTGGCTTAGATGAGCCCTCTTACACTCCCAAGCCAGCCACACATCTCTGCTCTCTCTGTGACAGAGCC
 CAACAGCCATGGGTACCACTTGAAGACCTTCACTCAACTTCAACAGCTCTCACTCTCAGATATTCAACAGAT
 ATGGGCAAGGGCTCAGCTCACTTCACTTCCACCGAGGGGGTCTCTCAGCACTTGGCTCAAGCCTTGTTCAGAG
 GAGCAGCATGGGCCCTTCTACTTGGGTGCCAAGCTGATCTCCCTCAGGGCTGAGAGAGGATGGGGCAGCACTG
 GTGTGGACACCACTTCACTCTACCACTTACCACTTGGGCCCTGGGGCTGGACATACAGCACTTTTACTGGAG
 CTGAGTCACTGACCATGGTGTCAOCCACTTGGGCTCTTATGTCTTGAACAGGATAGGCTCTTCACTCAATGG
 CTATGCAOCCAGATTTATATCACTCGGGGCGAGTACAGATATTAATTTCACTATTCACTTGAAGTCACTGAT
 ATCCAGAGCCCACTTCTCAGAGTACATCACTCTGCTGAGGGACATCCAGGACAGAGTCAACACACTTACAAA
 GGCAGTCAACTACATGACACCTTCCGCTCTCTGCTGGTCAOCCATGGACTCCGTGTGGTCACTGT
 CAGAGCACTTGTCTCTCTTCACTTGGACCCCAAGCTGGTGGAGCAGTCTTCTTAGATAGAGCCCTGATGCTCT
 CATTCATTTGGGCTTGGGCTTCCAGTTCACAGTGTGGTGGACATCCATGTGACAGAAATGGAGTCACTCACTTATCA
 CCAACAGCAGCTTCCAGCACCCAGCACTCTTACCCGAAATTTCACTCTCAGCACTCATCATATTCCAGGACAA
 AGCCACAGCAGCACCACCAATTTACAGAGGAGCAGAGGAAATTTGAGGATGGCTCAACCACTCTTTCAGAA
 ACAGCAGCATCAAGAGTTATTTTCTGACTGTCAAGTTTCACTTCACTTCACTCTGCTGCTCCCAACAGGACACACAC
 GGGTGGAGCTCTGCTGTATCTCTGCACTTCCGCTTGGCTGGAGTGGAGTGGAGTGGAGTGGAGTGGAGTGGAGT
 GCGGATGACCCGGAATGGTACCCAGCTGCAAGATTTCACTCTGGACAGGAGCAGTGTCTCTGGTGGGATTTCT
 CTCCCAACAGAAATGAGCCCTTAACTGGGAATTTCTGACTTCTCTCTGGGCTGTCACTCTCTATGAGGATTTCT
 GGACTCTGGGATCACTCACTGCTGATCTGCGGTGTCTGGTGGCCACCCGGCGGGAGAGAGAGAGAGAGAG
 ATACAGCTTCCAGAGCTGTGCAAGGCTTACCACTGACACTGAGCTGGAGGATCTGCACTTGAATGGAG
 TGGCTGTGCTGGGTTGCTTTTCCCCAGCCAGGGTCCAAAGAGGCTGGCTGGGCGAGAAATTAACCATATT
 GGTGG

FIGURE 52

GCGCGGGCAGGTCGCTGATAGCCAGTCTCTGCTCCAGAGAGGGAGGCGGAATAAACTTATTCATCCCGGGAAC
 CTGGGGTAAAGTGTGTGTGTTTTCACAACTTAAAGGCTTCACGAGCCCTGCGCTGAGACAAATTTTCGATCTCCGGA
 GGAGCTCTCCAGAGATCCGAGATTTGCTGATCTTCCTGTTTGGCTAGAGAGGGCTCCGAAACGACCTCTTGACACAGG
 GAACCTGGGCTGTAAACCACTGGTTTTCAGATTGTTTCTGGTGTGTTTGGTGTAGGGCTGAATTTTTCCTCTTT
 GTGGATGCTTCCGGAATATGAGAGGGCCGCAAAATCTACTACACAGAGAAATCCCTTGGGTCAACATTTGGC
 CTGTCGCCGAGGCTGCTGCTCTGCTGCTTGAATTTTAACAGCACGCTGATCGTCTTCCTGTGTGTGCGCAATCTGC
 TGTCTCTCTGAGGGGCACTGCTGATTTTTCGACGCCGACACTGAGAAAGCABTTGGATCAGACACCTCACTCTC
 CACAGAGCTGGTGGGCTATATGATCTGCTGCTACATACAGCTATTTCACCTCATTCGACACACCTGTTTAACTTTGACTG
 CTTAGACAGAGAGGCGACAGGCGACAGATGGCTCCCTTGCTCCATTTCTCCAGCTCTCTCATGATGAGAGAAA
 AGGGGGGTTCTTGGCTAAATCCCATCCAGTCCCGAAACACGACAGTGGAGTATGTGACATTCACAGAGCTTGTCT
 GGTCTCAGCTGGAGTGATCTGACATAGCTTGGATTTCTCATGTTAACTTCAGCTACTGAGTTCATCCGAGGAG
 TTATTTTCAGAGTCTCTTGGTATACTACCACTCTTTTATCTTCTATATCCTTGGCTTAGGGATTACGCGCATTTG
 TGGGAATTTGTCGGGCTCAACAGAGGAGAGAGCTGAGTGGAGTCTCTCGCAGGTGTGCGAGATCTTTTGAAG
 ATGTGGGATGATCTGACTCCCACTGTAGGCGCCTTAAGTTTGAAGGGCATCCCCCTGAGCTCTTGGAACTGGAT
 CCTTGCCACCGGTCTCTTTTATCTGTGAAGGATCTCCGCTTTTACCGCTCCGACAGAGGTTTGTGATTA
 CCAAGCTTGTGTATGCACCTACCCAAAGTTTGGAAATTCAGATGAACAGCGTGGCTTCAGCTCGGAAGTGGGG
 CAGTATATCTTTGTTAAATTTGCCCTCAATCTCTCTCTGGAATGGCATCCTTTTACTTGTAGCTCTGTGCTCCAG
 GGAAGATTTCTCTCCATTCATATCCGAGCACAGGGGACTGGACAGAAAATTCATTAAGGGCTTTTCCGAATAC
 AATATTCACCAATTCACAGGATTAAGTGGATGCTCCCTTTGGCACAGCCAGTGGAGGATGTTTTCAGATATGA
 TGGCTCTGCTGGTCTGGTGGACAGGATTTGGGCTCACCCCTTTGCTTCTATCTTCAATCCATCTGGATACAAAT
 CCAGTCTGGACAGCACAACTCCAAACAAAAGATCTATTTCTACTGGATTCGAGGGAGACAGCTGTGCTTT
 CTGTGTCACACAGCTATGTACTTCCCTCGACAGGAGATGGAGGAATTAGCCAAAGTGGGTTTCTTAACTAC
 CAGTCTCTCTCACCGGATCGGACAGCATATTTGTGGTCAATGACATTAATTTTGCACAGGCGCACTGGACAT
 CTTGACAGGCTCTGAACAGAAACCTCCTTTGGAGACCAATGTGGGACAATGAGTTTTCCTCAATAGCTACTCT
 CCGACCCCAAGTCGTAGTGGAGGTTTCTTATGTGGGCTCGGACTTTGGCAAGAGCTCTGCGCAATGTCTGT
 CACCGATATTCAGCTCTGGATCTAGGAAGGTTCAATTTCTACTTCACCAAGAAAATTTTGGATTTATGGAAAT
 AAGGACGGTAATCTGCGATTTTGTCTCTTTGGATCTTCAGTAATTTGAGTTATAGGAATAGGAGCTATCTGCA
 TTTTGTCTCTTTGTATCTTCAGTATTTACTTGGTCTCGCTCAGGTTTGAAGCAGTCACTTTGAGATAGGAATGTG
 CCTCTCAAGCCTTGACTCCCTGGIATCTTTTTTGTATTCGATTCACACTTCGTTACTGAGCTCAGACACTTA
 AGAATCTCTGAGGATCTTAAATTTCTGAGATTTCTTAAGGCGCTTGAATCCTTCTCAGAAAATTAATCTGTAAAT
 CTTTCTGGACAGCCATGACTGTAGCAAGGCTTGATAGCAGAGGTTTGGTGGTTGAGATTTATACAATTAATCC
 AGAGATTTCTATCATTTCCAGTGTACCATCTCTGAGTTTGGTTTGTATCTTTTGTCCCTCCACCCCCAC
 TGTATGGCTTATCCAGTGTGACAGCAATTTATTTTGTGCTCATCAAAATTAAGAGGATTTTCTCTTCA
 CTGTATGATGAGTCTTTTGTACTTCTTTTGGGCTCTCCCTTTGGGAAAGAAAATCTAGAAAGTATGTCAT
 TGAATTTGAATTTGATTAATTTGCACTGACCTATCTGATCTGTATTTATCTGTATAGAGCAATTTGTG
 AAACCTTGACATTCATCTTAGGATGATTTATTTAGTCAAGAGGAGCTCTTTATCTCATTAAGGGGATTTATTA
 AATCTGTATTTAAATTAATTAATTTATANTTTTCAATGATTTTGTGGACTCTACCTATATCTGCTAAGGAAT
 CATTCAGCTATTAATCATAGCAAAATGCCCTCTATCTCTATCAAGATGCTTTTATTTCTGCTATCTACCCAC
 CTGCGGCTACAGGACCACTGGCTCTGGGATGTAGCTGCTGACAGTGGAGGAGAGAGGCGCGAG
 GGCTCTTAGAGAGAAACCTTCACACTCTATTTGTGCTTCAGACAAATCTACTCTATTAAGATTAAGAAATGGTGT
 TCTGAATTTAGCATATATTAATTTATTTCTACCATTAAGTACCAAGATTAAGAAATGGTGTCTCTAT
 AGTTAGGACCTCTGCGGCTTGTGGGATAAACTGTTTGTGGTTTCTTTTGTGCTATGCTGAGCAGTCAAGAA
 TGGAGTCTGACTCATGTTGGGCTTAATCATGTTTCAATTTATACACAGTAABAACTAATGTTGTCTCTAAT
 ACATAGGGAGGATACCACTGCTTTGCCAATTTGTTTCCACCGGATTCAGCTATTTACAGTTTAAATAGGGCT
 TGGGAATTCGCAATGAACCTTTGAAGACATGTTCTTATTAGACACTACTGACCAATATGACACTCACTCT
 TGAATGCTTCTTTTGAAGATCTGAACCTTACACAGGTTCTCAATGAAGAGSCATCACTCTTGTGCTCCAT
 GCTCAATATTTTGAACACTCTCTCAGATATGAGGCTGCCAAATCAATTCCTGAGGAGTGTGATATTTA
 TGGGATGAGCATAATTTCTGATATATCTCATGTAATGATATTAATTAATTTCTATGATCCCAACTCCGA
 GTTGAATCGGATGAGCAGGATACACAGAAAGCTTCTCCTGCTCTTGAAGAGTTTCTTCTGCAATGTTA
 ATATGAATACCTTAATCTACCAATTTCTTATAATGTTTATATGAGTAGAAAAATCCCTCAATTTCTCTGTCTAC
 TCAAAATTTGATTATCT

56/162

FIGURE 53

CCCTTGGGCTCCAAACCACCTCTTTGACPAATTGGGAAACTGGGTGGTTAACCACCTGGGTTTCAGTTTGTGTTCTGG
 TTGTTTGGTTAGGGCTGAATGTTTTCTGTGTTTGTGGATGCCCTTCCTGAAATATGAGAAAGGCCGACAAATACTAC
 TACACRAGAAAAATCCTTGGGTCAACATTGGGCTGTGCCCCGAGCGTCTGTCTCTCTGCTTGAAATTTACAGGAC
 GGTGATCTGCTTCTCTCTGTGTGCGCAATCTGCTGCTCTCTCTGAGGGGACCTGCTCATTTTGCAGCCGACAC
 TGAGAAAGCAATTGGATCACACCTCACCTTCCACAGCTGGTGGCTATATGATCTGCCACATACAGCTATT
 CACATCATTTGCACACCTGTTAACTTTGACTGCTATAGCAGAGGCCGACAGGCCACAGATGGCTCCCTTGGCTC
 CATTCCTCCACGCTATCTCATGATGAGAAAAAGGGGGTTCTTGGCTAAATCCCATCCAGTCCCGAACACGA
 CAGTGGGATATGTGACATTCACAGCATTGCTGCTCTCACTGGGATGATCATGACAAATAGCCTTGATCTCATG
 GTAACCTCAGCTACTGAGTTCATCCGAGGATTTATTTGAGATCTCTTGGTATACTCACCACCTTTTATCTCT
 CTATATCTCTGGCTTAGGGATTACGGCATTGGTGGAAATGTCCGGGGTCAACAGAGGAGAGCATGAAATGAGA
 GTCATCTCTGCAAGTGTGCAAGTCTTTTGGAGTGTGGATGATCGTGACTCCCACTGTGAGGCCCTTAAGTTT
 GAAAGGCCCTCCCTGAGTCTTGGAGTGGATCTTGGACCGGTCACTCTTTATATCTGTGAAGGATCTCCG
 GTTTTACCGCTCCAGCAGAGGTTGTGATTACCAAGGTTGTTATGCACCCATCCAAAGTTTGGAAATGCGAGA
 TGAACAGCGTGGCTTCAGCATGGAGTGGGGCAGTATATCTTTGTTAAATGCCCCCTCAATCTCTCTCTGGAA
 TGGCATCCCTTTTACTTTGACCTCTGCTCCAGAGGAAGATTTCTTCTCCATTCATATCCGAGCAGCAGGGGACTG
 GACAGAAAAATCTCATAGGGCTTTGAAACACAAATATTCACCAATTCOCAGGATGAGAGTGGATGGTCTCTTTG
 GCACAGCCAGTGGAGATGTTTTCCAGTATGAGTGGCTGTGCTGCTGGTGGAGCAGGATTTGGGTCACCCCTTT
 GCTTCTATTTGAATCCATCTGCTACAAATTCAGTGTGCAGACCAACCTCAAAACAAAAAGATCTATTT
 CTACTGAGTCTGCAGGGACAGAGGTGCTTTTCTGGTTCAACCACTGTTGACTTCCCTGGAACAGGAGTGG
 AGGAATTAGGCAAGTGGGTTTTCTAAATACCGTCTCTTCTCACCGGATGGGACAGCAATATTGTTGGTCAT
 GCGAGCTTAAACTTTGACAGGGCCATGACATCGTGACAGGTCTGAAACAGAAAACTCCTTTGGGAGCCAAT
 GTGGGCAATGAGTTTTCTACATAGCTACCTCCACCCCAAGTCTGATGTTGGGAGTTTCTTATGTTGGCCCTC
 GAGCTTTGGCAAGAGCGCTGGCBAATGCTGTCACCGTATTTCCAGTCTGGATCTGAAAGGTTCAATCTAC
 TTCAACAAAGAAAAATTTTGAATTATAGGAATAAGGACGGTATCTGCTATTTGTCTCTTTGTATCTCAGTAA
 TTTACTTGGTCTCGTACGTTTGGAGCTGACCTTAGGAAG

57/162

FIGURE 54

GGGCTCCAAACCACCTCTTGACAAATGGGAAACTGGGTGCTTAAACACTGGTTTTCAGTTTGGTTCTGGTTGT
TGGTTAGGGCTGAATGTTTTCCTGTTTGGTGGATGCCCTTCCGAAATATGAGAGGGCCGACAAATACACTACAC
AAGAAAAATCCTTGGGTCTTGGAGTGGATCCTTGCACCGGTCATTCTTTATATCTGTGAAAGGATCCTCCGGT
TTTACCGCTCCGAGCAGAAGGTTGTGATTACCAAGGTGTATGCRCCCATCCAAAGTTTGGAAATTCAGATG
AACAAACCTGGCTTCAGCAATGGAGTGGGGCAGTATATCTTTGTAAATTGCCCTCAATCTCTCTCCGGATG
GCATCCTTTTACTTTGACCTCTGCTCCAGAGGAAGTTTCTTCTCCATTCTATCCGAGCAGCAGGGGACTGGA
CAGAAATCTCATAGGGCTTTCCGAAACAATATTCAACCAATCCGAGGATTGAAGTGGATGGTCCCTTTGGC
ACAGCCAGTGAGGATGTTTCCAGTATGAATGGCTGTGCTGGTGGAGCAGGAAATGGGGTCACCCCCCTTGC
TTCTATCTTGAATCCATCTGGTACAAATTCCAGTGTGCAGACCCACAACTCAAAACAAAAAAGGTGGTCTATG
CAGCATTAACTTTGACBAGGCCACTGACATCGTGACAGGCTGAACACAGAAAACCTCCTTTGGGAGACCAATG
TGGGACAAATGAGTTTCTACAAATAGCTACCTCCGACCCAGTCTGTAGTGGGAGTTTCTTATGTGGCCCTCG
GACTTTGGCAAAAGAGCCTGCGCAATGCTGTACCGATATTCAGTCTGGATCCTAGAAAGGTTCAATCTACT
TCACAAAGAAAAATTTTGGAGTATAGGAATAAGGACGGTAATCTGCAATTTGTCTCTTTGTATCTTCAGTAAT
TTACTTGGTCTCTGTCAGTTTGGAGTCACTTTAGGA

58/162

FIGURE 55

GGGGTCCAAACCACCTCTTGACAAATGGGAAACTGGGTGGTTAACCACCTGGTTTTTCAGTTTTGTTTCTGGTTGTT
TGGTTAGGGCTGAATGTTTTCTGTTTTTGGATGCGCTTCCTGAAATATGGAAGGCCGACAAATACTACTACAC
AAGAAAAATCCTTGGGTCAACATFGGCTGTGGCCGAGCGTCTGCTCTCTGCTTGAATTTTACAGAGCAGCTGA
TCCCTGCTTCTGTGTGTGCGAACTGTCTCTCTCTGAGGGGGCACCTGCTCATTTTGCAGCCGACACTGAGA
AAGCAATTTGGATCACAACCTCACCTTCCACAAAGCTGGTGGCCATATGACCTGCTACATACAGCTATTCACAT
CATTTGCACACCTGTTTTAACTTTGACTGCTATAGCAGAAAGCCGACAGGCCACAGTGGCTCCCTTGGCTCCATTC
TCTCCAGCTATCTCATGATGAGAAAAAGGGGGTTCTTGGCTAAATCCCATCCAGTCCCGAAACACAGACAGTG
GAGTATGTGACATTCACACGCAATGCTGGTCTCACTGGAGTGATCATGACAAATAGCCTTGATTCTCATGGTAAC
TTCAAGCTACAGATTCAATCCGGAGGAGTTATTTTGAATCTTCTGCTATACTACCCACCTTTTATCTTCTATA
TCCCTTGGCTTAGGGATTCACGGCATTTGGTGGATTGTCCGGGTCAAACAGAGGAGAGCATGAATGAGATCAT
CCCTGCAAGTGTGCAGAGTCTTTTGAGATGTGGGATGATGTGACTCCCACTGTAGCGGCCCTAAGTTTGAAGG
GCATCCCCCTGAGTCTTGGAGTGGATCCCTTGCAACGGTCACTTTTATATCTGTGAAGGATCCTCCGGTTTT
ACCGCTCCGACGACAGAGTTGTGATTACCAAGTTGTTATGCAACCCATCCAAAGTTTTGGAATTCAGATGAAC
AAGCGTGGCTTCAGCATGGAAGTGGGGCAGTATATCTTTGTTAATTCGCCCTCAATCTCTCTCTGGAGTGGCA
TCCCTTTACTTTGACCTCTGCTCCAGAGGAAGATTCTTCTCATTCATATCCGAGCAGCAGGGGACTGGACAG
AAAACTCATAGGGCTTCCGACCAACATATTCCCAATTCACAGGATTGAAGTGGATGGTCCCTTTGGCACA
GCCAGTGAGGATGTTTTCCAGATGAGTGGCTGGCTGGTGGAGCAGGAATTTGGGTCACCCCCTTTGCTTC
TATCTTGAATTCCTCTGTTACAAATTCAGTGTGCAGACCCACACCTCAAAACAAAAAGGTTGCTCATGCGAG
CATTAACCTTTGACAGGCCACTGACATCGTGACAGGCTGAAACAGAAAACTCCTTTGGGAGACCAATGTGG
GACATAGAGTTTTCTACATAGCTACCTCCACCCCAAGCTCTGTAGTGGGATTTCTTATGTGGCCCTCGGAC
TTTGGCAAGAGCCTGCCCAATGCTGTCAACGATATTCAGTCTGATCCTAGAAAGGTTCAATTCACCTCA
ACAAAGAAATTTTTTGAATTTATAGGAATAAGGACGTAATCTGCATTTTGTCTTTGTATCTTCAAGTAATTA
CTTGGTCTCGTCAGGTTTGACAGCTCACCTTAGGAG

FIGURE 56

GGACTGCTTTGTAACTGCTAAGATTGCAGACAGAAATAGCACACAACCACTGTGAGCTGTATGCGNTTCAGAAA
CCAGAGACCAATTTTGTCTACCTTCATTAACTCASTTGTCTCAGATAGAAGGAAATGSCATCTGGTCTCTGTCTCT
TCTCATCTTAAATTTTGGAAAAATATTTTCTCTATGGGGGTGGACAGGATGTCAAGTGTCTCCCTTGGCTATTTTC
CCCTGTGGGAGACATCACAAAGTCTTCCCTCAGCTCTTGTCACTGTAAAGGTGTGAGGACTGSGGGANTCAGGC
CGATGAGGACCACTGTGAGACACCAATGGATGGTCCATGCAATTTGACAAATATTTTGCCAGTTACTACAAAA
TGAATCTCCCAATTTCTTTTGAGGACAGAAACACTGATGTTTGGTCTGGTTCGTGCCAGTGCATATCTCTTTGC
CAAGGTCTGGAGCTTGACTGTGATGAAACCAATTTACGAGCTGTTCATCGSTTCTTCAATGTGACTGCAAT
GTCACTTCAGTGGAACTTAAATAGAAAAGCTTCCCTCGATGGCTCAAGAATTATCATGATCTTCAGAGAGCTGT
ACCTGCAGAACCAATAAGATTACATCCATCTCCATCTATGCTTTCAAGGACTGAATAGCCTTACTAACTGTAT
CTCAGTCTAACAAGATACCTTCTCGAAGCCGGGTGTTTTTGAAGATCTTCACAGACTAGAAATGGCTGATAT
TGAGATTAATCACCTCAGTCGAAATTTCCCCACCAACATTTTATGGACTAAATCTCTTATCTCTTATGCTCTGA
TGATTAACGTCTCCACCCGTTTACTTGATAAAGCTCTCTGTCACACATGCCAAGACTACATTGGCTGAGCCCT
GAGGCGAACCAATATCCATTAATTTAAGAAATTTGACTTTTATTTCTGCACTAATTAAGTCTTTTACTGATGAG
GAAACACAAATTAATCACTTAATGAAATACTTTTGCACTCTCCAGAAATCTGGATGAATGGATTTAGGAA
GTAATAAGATTGAAATCTTCCACCGCTTATATTCAGAGACCTGAAGGAGCTGCACAAATGGAATCTTCTCTAT
AATTCCAATCCAGAAATTCAGCAACCAATTTGATTAATCTTGTCAACTCAAGTCTCTCAGCCTAGAGGGAT
TGAAATTTCAATATCCCAACCAAGGATGTTTAGAAGCTCTTATGAATCTCTCTCACTATATATTTAAGAAATTC
ACTACTGTGGGTATGCAACCATATGTTCCGAGCTGTAAACCAACACTGATGGAATTTCTATCTCTAGAGAACTC
TTGGCAAGCACTTATTCAGAGAGTATTTGTCTGGGTGTATCTGCACTTACCTGCTTTGGAAACATTTTGTGCA
TTGCACTGCACTTATATCAGGTCTGAGAACAAAGCTGTATGCCATGTCAATCAATTTCTCTCTGCTGTGCCGAC
GCTTAATGGAAATATATTTATCTGTGATCGGAGGCTTTGACCTAAAGTTTCTGAGGAATACAAATAGCATGG
CAGCTGTGGATGGAGAGTACTCAATGTCACTTGTAGGATCTTTGGCCATTTCTGCCACAGAGATATCAGTTTT
ACTGTTAACTTTCTGACATGGAAAAATACATCTGCATTGTCTATCCCTTTTGAATGTGTGAGACCTGGAAAAAT
GCAGAACAAATACAGTTCTGATCTCAATTTGGATTACTGGTTTTATAGTGGCTTTCAATTCATTGAGCAATAAG
GAATTTTCAAAACTACTATGGCAACCAATGGAGTATGCTTCCCTCTCAATTCAGAGATACAGAAAGTATGG
AGCCCAAGATTTATTCAGTGGCAATTTTCTTGGTATTAATTTGGCCGCAATTTATCATCATAGTTTTTCTCTATG
GAAGCACTTTTATAGTGTTCATCAAGTGCCTATACAGCACTGAATACGGAATCAAGTTAAAAAGAGATG
ATCCTTGCCAAACGTTTTTCTTTATAGTATTTACTGATGCATATGCTGGAAATCCATTTTGTAGTGAATTT
TCTTTCACCTGCTTCAGGTAGAAATACCAAGGTACATAACCTCTTGGGTAGTGATTTTATCTCGCCATTANCA
GTGCTTTGAACCCAAATTTCTATACTCTGACCAAGACCAATTTAAGAAATGATTCATCGGTTTTGGTATATAC
TACAGACAAGAAAAATCTATGGACAGCAAGGTACGAAACATATGCTCCATCAATTCATCTGGGTGGAAATGG
GGCACTGCAAGAGATGCCACCTGAGTTAATGAAGCCGGACCTTTTGCATACCCCTGTGAATGTCACTGATTT
CTCAATCAACGAGCTCAATTCCTATTCCTGA

60/162

FIGURE 57

TAGAGATCCCTCGACCTCGAGCCACGCGTCCGAGGAAGAAAAAAGAGGAAATGGAAAGGACAGAGAAAGGAA
 ATGGGAGTGGAGAGGAGGAGGAGCTGCTTTGTAACTGCTAAGATTTCAGACAGAAATAGCACACACCCACTGTGA
 GCCTGTATCGGATTTCAGAAACCAAGACCAAAATTTTGGTCACTTTCATTAATCACTGTGCTCAGATAGAAAGGAAATG
 ACATCTGGTTCTGTCTTTCTCTACATCTTAATTTTGGAAAAATATTTTCTCATGGGGGTGGACAGGATGTCAA
 GTGCTCCCTTGGCTATTTTCCCTGTGGGACATCACAAAGTGCTTGCCCTCAGCTCCTGTCACTGTACCGTGTGG
 ACGACTGCGGGAATCAGGCGGATGAGGACAGCTGTGGGAGACAAACATGGATGGTCTCTGCAATTTGAGAAATAT
 TTGGCCAGTTACTACAAATGACTTCCCAATATCCTTTTGAGGCAGAAACACCTGAATGTTGGTCCGGTCTGT
 GCGCTGCAATGTCTTTTGCAGAGTCTGGAGCTGTGACTGTGATGAAACCAATTTACGAGCTGTCTCCATCGGTTT
 CTTCAAATGTGACTGCAATGTCTACTTCAGTGGAACTTAAAGAAAGCTTCTCTGATGTGCTTCAGAAATAT
 CTGATCTTTCAGAGCTGTGACTGCAAAACATAAGATACATCCATCTCCATCTATGCTTTTCAGAGGACTGAA
 TAGCCCTTACTAACTGTATCTCACTCATACAGAAATACCTTCCGAGGCGGGGTGTTTTGAGATCTTTCACA
 GACTAGAATGGCTGATAATTCAGAAATATCACTCACTCGAATTTCCGCCACCAACATTTTATGGACTAAATCT
 CTATTTCTCTTGTCTCTGATGAATAAGTCTCTCACCCGTTTACCTGATAAACCTCTCTGCAACACATGCCAG
 ACTACATTTGGCTGGACCTTGAAGGCAACCATATCCATATTTAAGAAATTTGACTTTTATTTTCTGCGATATTT
 TACTCTTTTATGTGATGAGGAAAAACAAATTAATCACTTAATGAATACITTTGACCTCTCCAGAACTG
 GRTAATTTGGATTAGGAAAGTAATAGATTGAATCTTCCACCGCTTATATTCAAGGACCTGAGGAGCTGTGC
 ACATTTGAATCTTTCTCATATATCCAAATOCAGAAAAATCAAGCAACCAATTTGATATCTTTGCAACTCAAGT
 CTCTCAGCCTAGAGGGGATTGAATTTCAATATTCACAAAGGATGTTTAGACCTCTTATGAATCTCTCTCAC
 ATATATTTTAAAGAAATTCAGTACTGTGGGTATGCACCACTGTTCCGAGCTGTAAACCAACACATGATGGAAT
 TTCTATCTCAGAGAAATCTTTGGCAGCATTATTCAGAGAGTATTTGCTGGGTTGTATCTCAGATTACCTGCT
 TTGGAAACATTTTGTCTATTTGCTATTTGCTATGGACCTTATCAGGTCTGAGAACACAGCTGTATGCCATGTCAATCAT
 TCTCTCTGCTGTGCGGACTGCTTAATGGGAATATATTTATCTGTGATCGGAGGCTTTGACCTAAAGTTTCTGTCG
 AGAATACANTAGCATGCGCAGCTGTGGATGGAGAGTACTCATTTGTCAGCTTGTAGGATCTTTGGCCATCTGT
 CCACAGAAGTACAGTTTACTGTTTAACTTTCTGACATTTGGAAMATACATCTGCTTGTCTATCTCTTTTGA
 TGCTGAGACCTTGGAAATTCAGAAACATTAAGTTTCTCATTTGCTATTTGCTATTTGCTATTTGCTATTTGCT
 CATTTCCATTTGACCAATTAAGGATTTTTCANAACTACTATGGCAACATTTGAGATTTGCTCTCTCTCATTCAG
 AAGATACAGAAAGTATTGGAGCCAGTTTATTCAGTGGCAATTTTCTTGGTATTAATTTGGCCGCAATTTATC
 ATCATATGTTTTTCCCTATGGAAGCATGTTTTATAGTGTTCATCAAGTGCCATAACAGCAATGAAATACGGA
 TCAAGTTTAAAAAGAGATGATCCTTGCCAAACGTTTTTCTTATAGTATTACTGATGCAATTAATGCTGGATAC
 CCAATTTTGTAGTGAATATTTCTTCACTGCTTCAGGTAGAAATACCGGTACCACTAACCTCTTGGGTAGTGATT
 TTTAATCTGCGCCATTAAACAGTCTTTGAACCAATTTCTATACTCTGACCACAAGACCTTTAAAGAAATGAT
 TCATCGTTTTTGGTATTAATTCAGACAAAGAAAAATCTTAGGACAGCAAAAGGTGAGAAACATATGCTCCATCAT
 TCATCTGGGTGGAATATGGGCCACTGCGGAGATGCCACCTGAGTTAATGAGCGCGGACCTTTTCACATACCCC
 TGTGAAATGTCACTGATTTTCTCAATCAAGGAGACTCAATTCCTATTCAGTACCTGAAATCAATTTCTCTC
 GAGAGCAATCTGTGGGGTCTTCTATGAGGATTTTACTGTTGAAATGAATACCAAAAAATTAATTTATAT
 AATAGCTAGATTAATTAATTTTACAGGACATGAGGAAAAATTAATTAATGACTTAATCTCTTACAAAGGGAGATTA
 TTATACCAATTAATTAATTAATTAATTAATTAATTAATTAATTAATTAATTAATTAATTAATTAATTAATTAAT
 ATTCATTTTCTACATGCAATTTATTAAGTACCCACTACTATGTGCTAGCAATTCGAATATAGTCTTGGAGTA
 GAGGTCAGAACTTTCAATCTGTAGTGTGTTTTAATGACAAAGACTATACAAAGCTCCATTCGAGCTTCT
 AGTTTAAAGTAGAGCTTTTACCTGTCTGTGCTACAGCAAGAAATCATAGGCACCTTTAAATTAAGGTTTTAAGGT
 TTGGAAT

FIGURE 58

GATCCATTGCTGCTGGCGGGGATTCTTTATPACTGGAGGAGGAGGAGGGGGAGAGTGCCTCCCGCTGGGGGAGC
ATGGGGCGCTGGCTTCGAGGCGCGCTGCTGCTGGCGCTCCTGTGCTTGCTGCTTTTGCGGAGAGCGTGTGGTGAG
 AGTCCCCACAGCAGCAGCCCTGGTTTCGAGTGAGTGGGCACTGAGCTGGTCTACCCCTGCGAAGCTCAGTGACTGTTGATG
 GCCCCAGCGAGCAAACTTTGACTGGAGCTTCTCRICTTTGGGGAGCAGCTTTGTGGAGCTTGCAAGCACTGG
 GAGGTGGGTTCACAGCCCACTGTACCGAGAGCGGCTGCGAGAGGGGCGAGATCTCTTAAAGCGGACTGCCAA
 CGAGCGCTGGAGCTCCACATAAAGAACTCCAGCTTCAGACCAAGGCGCACTACAAATGTTCAACCCCGAGCA
 CAGATGCCACTGTCCAGGCAAACTATGAGGACACAGTGCAGCTTAAAGTCTGCTGCGCGACTCCCTGCAGCTGGGC
 CCCAGCGCGCGGGCCCCCGCGAGCCTGAGGCTGCGGGAGGGGGAGCCCTTCGAGCTGCGCTGCGACCGCGCTTC
 CGCTTGCGGCTGCACAGCAGCTTGGCGCTGCTGTGGGAGGTGCACCGCGGCCCGCGAGGCGAGGCGCTCTCG
 CCCTGACCCACGAGGGCAGGTTCCACCCGGGCTTGGGTACGAGCAGCGCTACACACATGGGGAGCTGCGCGCTC
 GACACCTGGGCGAGCGAGCTTACCGCTCTCTCATGTCCCGGCTCTGTCTGCGGACCGAGGCTCTCTACAGGTG
 TATCTCTCAGCGAGTGGATCCCGAGCAGGGCACTGGCAGGAAATCCAGAAAGGCCGTGGAGTTGCCACCG
 TGGTGATCCAGCCGACATTTCTCGGAGCAGCTGTGCGCAAGAAATGTGTCTGTGGCTGAAGGAAAGAACTGGAC
 CTGACCTGTATCATCTACACAGCAGCCGAGCGGATGACCTCGCGCGCGAGGTGAGTGGTCTTCAAGCAGGTGCC
 TGACAGCACCTTACCTGGCTCCCGCTGTTGGCGCGCTTGCAGCTGATTCCTGTGTGCACAGCTCGCTCATG
 TTGCTTTGAGTCTATGTGGATGCAGCCTCTTACCATTTACTGGTTCCGAGATGTAGCAAGAAACTCTGTGCTAC
 TATTACTGCCAGTGTGCTGTGGGACCCCGACACAGAGGAGCTGGCACAAAGTGCAGAGGCGCTGTCTTC
 CCCAGCTGTGTGGGTGTGACCTGGCTAGAACCAAGTACCAAGGTGTACCTGAAATGCTTCCAGGTTCCCGGCT
 TTGCGATGAGCCCCACAGGCTCGGCTGCGGGTGGTGGACAGAGAGTGGGGAGGCGANTGTCCGATTCAGC
 GTTTCGTGGTACTACAGGATGAACCGGCGCAGCGCAATGTGGTGACCAAGAGCTGCTTGCATCAATGGACGG
 GGCATGGACCAAAATATGGAGAGGAGCAGCAGCAGCGGGCCAGGATGGAGACTTATTTTTCTAAGGAAC
 ATACAGACAGCTTCAATTTCCGGATCCAAAGGACTACAGAGGAGACAGAGGCAATTTATCTAGTGTGTGTCT
 GCTTGACCAACAGCGGGAACACAGCTGGGTGAAAGCAAGGATGTCTTCTCCAGCCTCTTAAATATTTTTG
 GGCTATGAGAGATTCCGTGCTTGTGGTGAAGGCGAGGCGAGCCAAAGCCTTTCCTTCTGCGGAAATACATTTG
 AGATGAGCTTGGCAAGTGTCTCCAGAGATATTAAGTCCGACAGCTACTGTGTCTCATCTAGGCTGAGAGGCT
 GTCGGAGACCTCTCCAGTCCCAATGAACAGAGTACATCATCTCTGGAGCAGGATCTGTGTGTGAGAGCTGGA
 GATTTGGACAGATGCTATCAGGGTGGATGGCGTGTGTTTACAAAAGTGACAGGAGATGAGTCCGCTATCGAA
 TGTACCAAGCTCAGGTCTCAGAGCGCAGGGCTGTACCGCTGCTGTGTGACAGCTGGTCTCTGTGAGGGCGAGC
 CTTTGGCGAGAGCAGCAACCACTCTCTCAATCTCTATTGAGATAGACTTCCAAAGCTCAGGTCTCTATATTAT
 TGGCTTCTGTGCTTACAGACACACCTCTGTAATTCGGGGAGATCTGATCAAAATTTGTTCTGTATCATCATCTTC
 AGGGAGCAGCAGCTGATCCAGATGACATGGCTTTGATGTGTCTGTGGTTTTCGGTGCACCTCTTTTGGCTGGAC
 AAGGCTCTCTGTCTCTCTCTCTCCCTGGATCCGAGGGGCTCTGTGAACACCTCCCGAGAGGAGCTGAGAGGCGA
 CCTGACGCTCGAGCGGCTGAGTGTCTGGATTTCTGCTGCAAGTGCTATGGCTCCGAGGAGCAGGACTTTGGCA
 ACTACTACTGTTTCCGTGACTCTCTGAGTGAAGTCAACCAAGTCTTCCGACAGAGGAGCAGACAGATCCACTCC
 AAGCCCCCTTTTATTAAGTGTGAAGATGAGTGTGTGAACCGCTTCAAGTATCCCTTGTGTGATGAGGCTCTCT
 GTTACAGGTCTATCGGGCTCTGTCTCTCTCATCGGTACTGCAGCTCCCACTGTGTGTTTGAAGAGGAGGTTT
 AGGAGACCTCGCGGAGCGCGCAGGCTCATGTGCTTGGAGATGGACTAGGCTGCGCGCGGAGGGAGATGACAG
 AGGACGTTCTAGGAGCAATGCGCAAGAGAGGAGAGTGTATTTTTAAACAAAGTGTGTACACTAAAGAC
 CAGTCTCTCTATCTCAGGTTGGGACTTGGCGCTCTCTCTTTTCTGCAATGTCAGAGTTCTGAGCGGAGCATGTT
 TACCGACACAGGCTCTCTCTCCACGCGCTTTCTGATGTAACAACTGAGTGTGTGTTTTCCAAAGTCCGAGT
 GNTAAAGAACTCCGCGCAGCAAAATGGATCTCGAGGGATCTTCCATACCTACCAAGTTCTCGCGCTGCGAGTCT

FIGURE 59

CCACGCGTCCGCGGTAATCACTTCTTGGAGGTGCCCTGCACGCCGCTCCTGGGAGCGAGCGGCTCCCGGGG
 GTCCGGGAGCCCACTCTCTCCGTGGTGTGTTCCATTGTGCTTCCCACTCTCGGAGGAGCTGACGTGCCAGCTCC
 CCGACGACCCACCAGGAGCGAGGAGGCTAGAGCCGGTCAAGGCACCTGGGCAAAATCCGGAGCGCTCGGAAGAT
 GTCAAGAGCCGATGCGTCCGCGCCAGCCAGGCGTCACTTTAGTGACAAACGAGGTGCCCGGTGGCCACGAGACGC
 CTTCTGGATGGGAGTTCTGAAGCCTACTGGCGGGTGTCTAGCCAGGAGGCGAGGCTGACATCTCTGTCTCCGG
 TGGAGGCCAGTACATCCAGGCCCAAGGCCAGGGGCCCGCTGTCCGCCAGAACCTTGGAGGGGCGGAGGCA
 GGCCCTAAGGAGCTGGACTCCAGCTCCCTACAGTCCGGCAGCTACTTCCCTGTGGCTCAGAGGCGAGCGAGCG
 GGCCCTACTGCAAGCTGGGCCCTCAGCTGAGAAAGCCCTACCTGAAGGAAAAATCCAGCGCCCACTGTGTACTCTCC
 AGACCGTCAAGCACAACAACATCAGAGACCTCGTCCGCGCTGCATCACCAGGACTAGCCAGGTCTGTGTCTCT
 CTGATGGATGTGTTACCGGATGTGGAGATCTTCTGTGACATTTAGAGGCGAGCCAGCAAGGCTGGGGTGTCTGT
 TTGTGTGCTCTCTGGACAGGAGGTGTGAAGCTCTTCCAGGAGATGTGTGACAAAGTCCAGATCTCTGACAGT
 AUCTCAGAGACATTTCCATCCGGAGTGTGGAGGAGAGATATACTGTGCCAAGTCCAGGCGAGAAATTCGTGTGGC
 CAAATCCGGAGAAATTCATCATCTCGGACTGGAGATTTGTCTGTCTGATCTTACAGCTTCACTAGGCTCTG
 CGGACAGGTGCACCGGACATCTCTCCAAGTTCACAGGCCAGGCGGTGGAGTGTGTGACAGGAGGTCTCCGCC
 AACTCTAGCTCTCTTCCAGGCTGTGATGTGGCTGAAGTCCCGCGGCTGGTGCAGCCCTGCCCGCCAGGAGCA
 GCGCCCGCCAAATGGCCGCTTAGCAGCAGCAGTGGCTCCCGCAGTACCCGACGCTCTCCAGCCCTCAGGCGG
 CGCTCCGGAGGAGCCACCCCGGTACCCGAGGTGTGTCCGCTCTTCAGGGCTCTTACGGGCTCTTACGGCCGCGCCAC
 ACCCGCTCTACCGCCCGGTTCCAGGCCCAACAAAGCCCTTGGGAGCCCGAGTCCCGAGGCTCACTCTCC
 CCGGCGCCACCGCGCGCCCGCGCTGTCTACAGCAACCTGGGGGCTTACAGGCGCAGCGGCTGCAAGCT
 GGAACAGCTGGGCTGGTCCGAGGCTGACTCCAACTGGAGGCCCTTCCGCGAGGCTCTCCCTCACTCTAGAA
 GGTCCCACTCCCTGCTGCTCCCTCCGAGGCCAGGCTGGGCACTCCCTGAGACCCAAAGACCCACCTCAAGAC
 GAGTGGCTGTGAGCACTTCCCTTGAAGAGACACTCAAAATCACTGCCATGGTTCAATGTTCCAGGCCCGAG
 GCCATCCACTTTCGCGGCCCCACAGTTCTTGGGTTCCCGGCTCTAGTTGAGCTGTGCGACATTCAGAGAG
 GTTCCAGGGGAGGTTGTGGGCGAGCTAGAGGACAAATCACTGAAACAGAGTCCCTGCTTCCAGAGATCATCC
 GGGGCTTTAATATTAATGGCCCAAACTCCGTAAAGACGAGGAATGCAGCCCACTTTACAAATGGGTAA
 ACAGAGGCACTGAGAGATAGATGGTAGTTTGTGACTTCTGGTCCCACTGCCAGGAGTGGGCTCACTCCCAAGA
 AATTCAGGAAGAAAGACTAGGAGAGAGGTGTGGAACTTTCTGATGTTCTGGGAGAGTTGGGGAATCTCTC
 CTCTTAGGAAGGCTAATACTAGGGTATCTTGGGCCCAATGATAGGGGTGAGGCCCGCAAGCCGCTTATCT
 ATGAGTTGTATGGGGAGGCTATCTGAAGCTGTAGCCACAGGGGTGACAGCTAGCTGAGGAGTTTGGGCTGTGG
 GTTGGACAGGCGAGTTAGTAGACTCAGATTTCTGCTCAAGAGGCTTGGGCTGGCTGGAGGCTCCCTGAGT
 CTGACTGGACCTAGGAGCTTGAGTTGTAGGGGCGAGGACTGGCCCACTGCACTGCCAGGCCAGTCTTGG
 CAGCAGGAGGCTCAGCTGTCCCAATCCAGGTGCCCTGAGCAGGCTGGTCACTCTGAGGAATTAATGCT
 TGAACCTCAAGGCCCACTATATCAATTTCTTCTCAATTCAGAGTGCCTCTTGTCTTCTGGGAGGAACTAGG
 TCTCTAGGGGACGCTTACCTGAGTGCAGAAATATAGGATGCTTAGAAAGCATACAGGAGGGCCAGCGCTG
 GTGGCTCATGCTTATCCCTCAGAACTTGGGATGTGAGGTGTGTGATATCTGAGTCAAGGTGAATTAATCT
 GGTCTCGAGACCGCTGACCAATATGCTGAACCCGCTCTACTAATAATACAAABATTAAGCTGACACAGG
 AGAATGGCTTAACCCAGGAAGCAGAGGTTGCATGAGCTGAGATTCGACCTGCACTCAGACTGGGCAACA
 AAGCAAGGCTCCGTACAGAAAAAATAAAAAA

[illegible]

64/162

FIGURE 61A

GAAAGACATACACACCTTCATGTATTCCTACCTGCAAGTCTCCCTAGAAAGCAGTTTTTGTASGTTGAACACAT
 GAGGCCCGGTATATTTGCAAGGAGGCTGTATTTTTTAGCAGACCTACCAACACACACTGATGTAGGAGGCTCATTA
 TTTTATTTCTCGAGGCTTTTATTTTTTCTTTAGAAAGTGTATTAATTAATTCAGGTGCTGCTTTGCTTCCAAA
 ACTGGGCGGTGAGTTCAACCAACACGACAAACAGCGCCAGCTCTCTCTGGCGCTCATGTGGAGTTTCTTGAAG
 AACCTATCTTTGTGAATGTATTAAGTGTCCACAGTGTATGCTTTTCCACACTAGAAAGAGAGAGTCCGAATGAACAC
 TTCCATGCAATGTGTGAACCTACACAGAAACCGGTGATTAAGATCACTGTCCACGACGAGACGACGAGGAGCTG
 GAGTCAGAGGCACTGTACCTGCTGCTACAGTGGCTCCAGGCCACAGAGAAAGGGGGCAATGAGTACGCCCTATGCG
 CAAGTGAACACTCTGTTCTGCTTCAGCAATATGCTTCATTTTCATGATTGCAGAGTCTGTGGTGGGCGCTATG
 CTGGAGGCTCTGCTCTCTGCTACAGATGCTGCCACCTCTTNAATTGACCTGACAGATTTCCTGCTCATCTCTCT
 TCCCTGTGGTGTGTCTATGCAAGGCTCTCTCTACAGGCTGACATTTCGATGGCAGGACGAGTACCTTGGTGG
 CTGCTGCTCCCACTGTGTGATCTGGGTGGTGAATGGCTGCTATGATGATCATGTTTCCAGCTGCCAGTGGCGCAACTTTGACTAACT
 GTGGTTTTGCGACCAAGAGTGCCTTGGACCAATACCAAGGAAGTACAGGCCAATGCCAGGCTCAGAGCTGCTTT
 TGTGATGCCCTTGGAGATCTTTTCAGAGTATCTAGTGTGTCTAATAGTGCATTTATTTCTATCTTAAGCCAG
 AGTATARAATAGCCGACCCCACTGCACTTCACTTTTCCATCTGCTCTTGGCAGGCAACCATCATATCTTTA
 AAGGACTTCCCATCTTACTCATGGAAGGCTGTGCCAAGAGAGCTGAATACAGTGGTGTGAAAGAGCTTATTT
 AGCAGTCGAGGGGTGCTGCTGTGACAGGCTGCACTTGTGCTCTACCAATGAATCAAGTAATFCTCTCAGC
 CTCATCTGCTGACAGCAGCCGCGGACAGGCAAGTGGTTCGAGGAATTTCTTAAGGCTTAGCAACAGC
 TTTACGATGCACTCACTCACTTCAATGGAATCTCCGATTCGAGGAGCCCGCATGCTCTTCTGTGCAAG
 CCGCTGTGACTAGCTCAGTCACTCAACCGCTCAGTTTCCCAATTTGACAGGCGACCTTCAAGAGTCTGTATGAG
 TTTCTGCTCATAGAAATAGGACCCAGAGGAAGAAATTCATGTCACTGGTGGCAAGTCAATTTATCATTTA
 TTTAGTCCCAATCCCAATGAGGAAGAGGCACTGAGATCCATCAATTCAGTATATATAGTCACTAGATCT
 GTCTTCGAATGCAAGAAATGTGTATATAGATTAATCTTGAGTGGAGCGAATACAGCTGTTTGTAACTATCGG
 CAGTACCAATTTCACTCTCCCTCCCAATATGCACTCTTGAGACACATAGGTAAATTTGAATCTAGGAAGTCT
 ACTAGAAATCTGGGAGGAGCAATAGTCACAAAATTTACCAAAACMTAGACACAAAAATAGAGGAGGCC
 AAGTCAGGAATAAAGTGCCTCTGTATGCTAACGCCACATAGAACTGGTTCCTCCACAGGCTGTAAATGTGA
 TTTTTTTTCTACTCTGAAATGAAATATGATGAAATACAGGAAGTCTCTCACTCAATTTTATTTATCT
 GTCAATTTTGGCAATTAATCCCTCTTATTTCTAATTTCACTTGTCTATTTCAAAATTTATATATCACTG
 TTTCAAGGAATATTTTCACTTCAACGAGTGGCTTAAACCTGGCAGCAGCAAGAAATCTGTTGTAGAGAGC
 CAGAACTCTCAAGAACAGCGCAGCAAAACATTCGAGTTCAGCCCBACAGATTTGTTGCCACAGATTAATTTGA
 AATTACCTGCAAGGAAGAAATAGCAGATGCAACCAATTCATTCAGGCGAGGAGTATGATCTGAGCACTGCT
 GTGCTAGACATTTGGGCTTACATTTGAATATTAAGAGGAATCAGAGCGAGCAATGCTCTGCTCTCTGGTGA
 CACTCTCACTACTCTGTGGAGGTAATCTGAAGTGTGAGGCCAATCTTGGAAATCTATGTCACTGGGT
 TGGTTTGGAAATCTGGACCTTCTGCAATTTTAAAGTTTACCAGAGATGCTCTCAAGATGAGGCAATAGCTATG
 AAGATGTGACACACAGAGTTCCTTCACTGGGACAGCTAGACATACATCACTCACTCAATATGATCATGA
 ATTGCAATGATGTTGTTGGGTATTAAGAGGAAACGATGGATTTGCCCGGATGGGCACTGGCCAGATGTTTAC
 GTCAATGAGGTGACAGCTCTCTGCACTTGAATTACATATGAGGCTCTCCAGAGAGCAGAGAGAGAGGA
 CAFTTCAAGCAAAAGAGACTAGGCACAGGACACTTATGTTTGTCTGTTAGCTTTTATGTTGAAGAAACAA
 ATCACTGTGTCGAAAGAACTCTCAACCGCTGATTTTTTAAATCTACATCTTTTGCACCTTTATGTTTGA
 GTATTGTAGAGACAGAGATGCTCTTAGATGATTTTTATGTTGTTGTAGACTCTACAGAGGTCTACAGAA
 CTAGCAGGCAATTAATTTTGTGAGCAATGATCTGAGGCTATATCTGAGGCTGTGCACTTAATTTATCAAT
 ATTTGTATTTTTTCTGAAATTTGAGGCGCAAGAAACATTCGATTTGACTGAGGAGGTACATCTGTGGCATC
 TGTGCAATCACTCAGCAGCACTGAAATTAATCACTTAGCATTTCTGCTGAGCTTCCCTGCTAGTAGAGCAAA
 TATACTCATCCCGCTCTGAGTGGCTGTGTAGGCAACCGCTAGGCTGAGCTTCTGCTGAGGAGCACTGATG
 GGCACATCGGGTCTCAAAATGGAAGAAATGTTTATGCCAATTCATCTTCTGCTGAGGAGCACTGATGAT
 GTTTTGTTTTCCCAATTTTATAGGAGCCCTTAAGAGATAGGCACTTCCCTGCTGAGGAGCACTGATG
 ATTCCTTCTCTGCTTTCTTTGAAATTCATGTTAGATTTGATTTAGTGTGAGGAGCTCCAGCTGCTTCC
 TAACTATATGAGAGAGATTTGTGTCAACCAAGTAATTTTCCAGGCCCGGGTATTTCTGTGTTCT
 CCGTAAATTTCTGCTTTTATGCTAGCTAGATTTGAAATCTTGAACAGTATGATTTATATGCAAACTGATC
 CAATCTATAAGAGGATTTTAAAGATTTGAGATGAAAAACAGATGTCTAGGCGCTTTAGGAGCTCCTCA
 TCAATTCGAGATTTCTGATCTCCCATTACCTTTCCCTGATGTGGTCAAGAACTCCAGGTCAGTGAGTGT
 GGAACTGTGATCTGATTTGATTTTACTTCAAGAGATTTGATTTCTCTCACTTCAAAACATTAATGATCTT
 TGTCTTTTTTTTGTATTTGATTTACTTTAAATCTGGGTCATATGTGGGAACATATGAGTTGTGATCAAT
 NTRCATGTGACATGATGTTGTTGCTGACTCAACCACTCTGATCTCACTTTTATGTTCTTCAAGAC
 ATCTGCTTCTGCTTCTCTGAGATGAAATCAGCTCAACTTACCAAGGCTCCATTTTAAATATGCTTCAAC
 ACCAGCACTTACTTCAATTTTCTGAGGCTCTGTTGATGTTTGAAGCCATAAGAGAAATTAAGCTTTCC
 ATGTTGTTTGGTTACAGATGGAATGGCAATGTTTCAAGCAGATGAAGAGGATTTTACATATTAAGATCA
 GTTCTGAGCTAGATTTGCTGAGTTGAGTCAATCTTACTCTCTCTTATGCTCTGCTGAGCTGAGCTTAT
 TAAATGCTGATGCTATCTTCTGATCAGTGAACCTCCCTATTCAAATGTGTGAGGATTTATTAATTAG
 CACACTAABAAAGTTGGAGAGGTCATAGCACTGTGTTGTCAGTACTTGAATGTTTATTTATGATGA
 CAACATGTCTGGGCAAGAAATTTAAATCATCTCACTTTTGAAGAAATTTGAATATCAACACCGTCCAC

CGCGGCGAGACGCTCTCTCGCCCGGGTCTCTGGAGAGTGCCTGCTGGAGCGGGCGCGCGCGCGGGAGATGCTGTGAC
GCTGGCGGACCGGACCCCTCGCGCTGAGACGGCGACACAGTGGCTGCTGAGCTGCTGTGTATCGCTGTGGGCGTCA
CTCTGGGCGACAGCCACACGACGATCTCTCGCTGTGTGGGGTCACTGCTGTGTGGGACACATGCCACCACCAAGAAC
GGCGTCTCTGGCGGGGACGAGGACCGGACCCGCGCTGGAGAGCGGAGACGACCGCTCTCTGGGCTCTGCACAAAGTGT
CAATGTGTAAAGATCTACGGAACCTGTTCAGCGCCGCTGCCCTCTCCAGCTTCCAGACACATCTATGTAGACCGAGT
CAAGCTGTAGCGCTCGGAGTGTCTATCACTATGACGACTATCTACTGAGCTCTACGGAGAGACCACTACACTCT
CGCGCCCGCGACCCCGCGAGTACGACGTGGCTCTAGAGAGCGACTCTGAGAGAGAGCTGTCTATCTCCCTCAGAA
TGTGTGTGTGGAGGGATGTCTGTGTAGAGAGCTCTGGAGACCTGGAGACAGAGGCTGGCACTTGGAGACAGGCGCCCA
AACTCCCTCATCTCTGGCTGGCTGTAGCTGTCTGAGCTCTGAGAGAGTGTGGCCATAGGACCGCGCTCTGTGTAGAGCTCAG
AGCCCTAAGAGAGCGAGCGCTCGACACACCTGGAGAGAGGCGCTGTGGTCTCCCGCTCGCGAGAGAGAGCTCT
CCAGAGCGACCCCTCGACGCTGACCTTGAGGAGCTGTGGAGCTGTCTCCGCTCTGAGAGCTGGCGAGAGCTCTCT
CTGGGCTGGAGAGGAGATCTGTGTGTCTCTAGGGGCTGCCAGTGTGGTGGAGCTAGAGACTCAGCGACAGAGGCT
CTCTCGAGAGCTGGAGAGAGGCTCTACTATCTATCACTACACTCTCCCGGAGCTGGACACGCGCTCTGTGGTGGTGTGA
TTAAGGCGAGAGACCTCTCACTCTTAACACTCAAGAGACCTCGGCGAGGAGATCTGTGTCAAGAGTCACTGT
AGTCAACCGAGCTCGAGAGCTCTGAGAGAGAGAGAGAGACTTAAGCAGCTAAGCAGACAGATCAACCCCTGTGGACAG
SAPATCATCTTTTGTGCTCTGACGACCTCTGTGGAGGCTCTCGGTGTGGAGCTGGAGAGCTGTGGGCGAGAGAC
ATTGAGGCGAGAGCTGTGGGCTGTGGCCATCGACGCTGGGCGCTGGACGCTGGGCTCTGAGCGCAGCCACTGTGG
GAGGAGAGCTCTAAAGAAACCTCGCGCGAGATCTGCATCTGGACACAGCTGCACCTCTGAGCTCGGCTCGAGCT
GGCTCCCTCTCTGGACAGCGCTGTGCCCTCTCTGCAACTCTCTCTCTGTGGCCCTTCTCCATCTCTGACATCCC
AGAGACAGATGACAGATCTGTCTTGGAGGCTGGGATGGCTCTCTCACTCACTCTCTGPTTCTAGAAATAGAC
AGACAGAGAGAGAGAGAGAGAGAGCTGGGCTCTCACTAGAGATGCAATTTGTCTCTCTCTTTATGAGAGAGGT
CTTTATTAAATCACTTCTTAATGCTGTTTATAGCTGGGTTGGCCAGCTAGAGAGAGTAAATGTGGAG
ATCATGTGTCAGAAAGAAATTTGCTCTTTGAAACACAGCAATCAAAAGATGACGAGCGAGTGTGAAGTATCT
CTGGGCTCACTCTAGAGTAGAGAGTGGCCAGCGTGGAGAGAGCTTAGGACAGCTCAATCAAGCTCAACTAT
CGAGCTCTCTGGTGTGGATTTCTGCTCGAAGAGCCGAGAGCTCTCTTTTAAACAGCTGTATGAGGCTGGAGCG
CACTGTTCTGTGGTGTGGATTTCTGCTCGAAGAGCCGAGAGCTCTCTTTTAAACAGCTGTATGAGGCTGGAGCG
ACTGTATGTGGAGAGATTTCTGCTTACAAATTTCCACACAGGTTTTPGGGCCACAGTCTCTGATGGAGCTCAAA
CACTGGTGCGAGCGAGTCCCAATGGCGACACCTCAACACTAGGCGGAAATCTGGGGGCTCAGCTTTTAAATT
AAATTATTAAATCTTAAATCTTAAATTTGTGTCTTCAATAGAGGCGGCTGCTCTGAGCTGAGATTTGTGCTTT
TATTGAGAAATTTTATGTTTATTTTCTTAAATATGAGTTTCTTATTTCTCTGGGAGAGCACTCCCTACAAAGAT
ACAGGTTGGGATCTCTGTGTGATCTATGGCTGGGTTCTGATTGTAGAGTCTACACCCACAGCTACCAAGAT
GACTCTGAGATGAGACCGTCTCTCTCAGCGTTCAGTCTCTCAGGAGGAATTTAGTATATGACTAGTGTCT
GACBCTGCTGCTCAGTGTAGGTAGAGAGAGAGACATTTAAAGAGAGAAATCAAGTCTTTTGCACATGTGGCTT
CGCTGTGCTGTGTTTAAATAGGTAATTAAGCAGCGCTAGGTTTGAATCTCTACTCTGTATTTCTAARAC
AAGTGTCCACATTTGTATTAATTAACATAATTAAGCAGCTCTGCTAGGAGATACAGTCTATACACTGAGACAGG
ATCTCTGGGTTCTGTGTGTGACATCTGCCCTTCAGCCTCTGAGCTGTGGCAGCTGTATAGATAGGATATATGACT
GGAGAGAGCTACCCACTGATGATATAGTATAGATAGAGAAATGCTGTCAAAACCTGTAGGCACTCTGTGTCAAAAC
AACTCTGTAGGCGGACACAGCGCTCTCTTATAGCTAGTATATTTTACACCTTTTTTTGTAGAGAGGATTTT
GGCTCTTTGTGGCCAGGCTGTGGAGTGCAGTGCAGCGATCTCGAGTCTCTGCAACTCTCGCGCTCCAGAGCTCAGCG
GATTTCTCTGTGTCAGCGCTCTGGGATCTGGGATCTGAGTGTGGCACTCAGACATGCTGCTGTATTTTGTACHT
TTTATAGAGATGGGTTTTCACATCTGTGGCGAGGCTGCTGCACTCAGAGCTCAGGTGCTACCCCTGTCCAGCG
CGAGCTCTCCAAAGATCTGTGTATATAGGCTGTGGCGACCGCGCGCGCTGATTTTGTCACTTATTTTGGGAGCG
AGAGATGCCAAAGAGTGGCAGAGAGACTGTGGCTTTCCAGAAACATAGGATTTGTGCTTTGGGCGCTCTCTTA
TTAATTTTAAATCTCTGGGCGCTCAGATCTCACTTCACTTCCCTTAAGACAGATTCFGGAGAGAGCTGG
TGAAGGCTCTACTTCTCTCAACAGCTCACTCACTTGGCCTCTCCCTGAGAACTTGAGCAGAGGCTTAATA
CTGTGTGGTCACTTTTCTTCTCTCTCAAGAAATAGAAAGGATAGAAATCTCTTACCACTCTCTGAA
AACAGAGAAATATCGATTCCTCTCTTCAAGAGAGTTTGTGATTTTGGAAATCTCTACTGAGGTT
GGCAGCCCTGCGAGTGTCTCTGTAGGCGTATGAGTGTGTTTATGATCTCTTAAATTTTGAAGATCTCT
CACACCTCTGCTTCTCTCTCTGTGGTGTGGTGTGAGTGTGAGAAACAAACATTTCTATAGCTGAGTCTGA
CGGACTCTCTCTTGTGGTATCTACTACTCGACCTAGAGAAATTTGGATCTAGACAAAGATCAGCAAGAT
ATGGCTCTTAATTAATCTGTGGAGCTGCTGTATGTATACCAAGAAATTTCAAGGTGGGCTGGCGGGCGCC
GATGGCGAATTTTCAACTGACCCCTCACTTTTGCTCATGAGACCTCTTCTATGCTCTCTTTTCTTT
TGGGGCGGGCGGGCGGGCGGGGGGGTCTCAAGTTTAACTCTTCCAGAGTCAAAATTAAGGTTGGCCCTGATG
GGCGGAGATTTCCGCGACAGAACTCTAGATGTAGGCTGAGCGTCACTTACAGGAGTACAGAGAAAGAT
ACTTTTGTAGGAGAGAGGTTGCTCTGTATGCTCTGTATCTTCAAGTCTGCTGGGATAGAGCTGTCTCTGTGGTCT
CTGTATATCTCTATATTTTGTGAGTATTAATGAAATTAAGATTTAGAGTGGCTGGGAGAGTGGCAGAAAGAC
ACTGCAATGGCTAAAAATTTAAGTCTAGCTGACTCTCTCAATGTTTAAAGCTCAGAGTGTCTAGCTCTCAAG
GTAGAAATCTCTAGCACTAGATTAATTAATTTGCTATCTGACCTCTGCTGCTGCTGTATGTATCTATCA
CTGATGAGAGAGATTAATTTGCTCTGTTTCCATCAAAATCGACCTTAGTGTATTTAAATTTCCGAGAGT
GGCAAACTGGCAATAAAAATTTTCACTGAGTCTTGGCATGCTTACCTGCTTACCTGACAGAACTTCTCTAT

67/162

FIGURE 62B

CTATCAAAATATAGTAACCTGAGCCTGGTGTGAAGTATCTCATCATTTTCGAAAGGAACACCTTGTGTGATGCCCG
TGAGCATTTCTAARANGGGTGTGAGGTAGAGGTAAAAATAAGGTGAGAGACCATTTCAGCANTGCCCTGTGTGCTC
AAAAAGGTGATCTGCTTCTTCTTCAGAGATTTCTACGGGGATAGAAAACCGGGGCTCTGCCCTCATTATCTG
TGRCTCCACCTCTGTGCATCAAAATCAATATCTATTTGTGAGCACTTATTTGATTAAAGACCTTGCATATCTCTGTC
CATTTTGATTTGAGTACCACTTTTGTGTGGGTGAATGACAAATCCTCCAAACAAAAGTGGGCACAGAGAA
TCAGCTAGGGAGACCGTTATTCAGGGTCCATTTCTCTTGGATGIAAAGGAGTCCCTGGGTAAAAATGTGGCTGTAA
CCTAAACCACTAGTCTCTGATTTGTTTCTGCCCTCTGTGTTTCTGTGTTGTCAAATGCTAAGTGTGGTGT
GCAGTCATGAACTAAGCACAAAAGGTGCATGAGACATTTGATGTCATATGCTGGTGTGACACTTTGGAGTAA
AAACCTTCAGTGGTAAATAAAAAATTTCCACAGGGGAAAAAABAAAAAABAAAAAABAAAAA

FIGURE 63A

[illegible]

69/162

FIGURE 63B

ATCCAAATAGTAAATTTTAAATATTTGTATTCTTGTTATTCTCGGAAGAAAGGCTTTGCTGTAGCACTTGGTATTTT
GCRAGTGGCTTTTAAACATTTCTTACTTACCGTATTTTCATAGAAGGGPAGGAAAAATGTAAGSTTTTACAGATAA
GCACCTTGCTTTGAACATGGAGGCATGTGGTATCATGGATTTCTTCACTAAATTTAGCTGTCCCTTAATCACAGAK
CCTAAGTAAATATATATATATTTTAGTGCATTTCTCCATCAGSANTGCTGGAGGTGCATTTTAAAGTTTTAAI
AAATAGTGTAGAAATGACCAATTTGCAGACTAATTTGTTCCATATTTGTACTTAAATGAGTTTTBARAGTTGAA
AAGGAATGACATATACANTCAATGCTATTTATTGTACCTCTGGGCTTACTCTCTAAAAATTTGAGGCTATC
GATTTTCTCTGTCAAGCTTTCAACTAATGTAAATATTTGAATATGTAAGCTATATTTTCATGTTTTTATAG
ATACACATGCAAGAAATACATATGTAAGAGTATTTCAACTATGGATATGTTTGATTTGGATATGCAACATCTC
AGTTCAAGCAGTACKCMATGTTTAAATGCAATGTAACGGTGCTGATATATTTGCTATATATATGCTGTG
TGCAATATAGCTGAATAGTGGTCAACCAAGAGAGATGACAGCTGTCTAAAGGTTTTTPTATTCATTTTATATAA
AACTGTTTACGATAGTACCTTTTCTTCTGCTGTTTAACTGGGTGTCNACTCCAAAGAGACATACACTTTTCTA
TTACTTCTATTGAAGATTTGGATTTTCATATTTTCACTGCTACTATGTCAGAAATGCTTTGATTTTATT
TTAATTCATACATCGGATGGCTTTTCCGGAGTGTTGTAATAAATTCATATCATATATATATATATATAT
AGGCAAGATCTT

70/162

FIGURE 64

GCCAACACTGGCCNAAAGGGATAGCTGTCCNAGGTCCTCCCCAGCACTGAAGAGCTCGCCTGCTGCCCTCTTGC
 GCGCGGGAAGCAGCACCCAGTTACCGCCCAACGCTTTGGCACTAGGATCCNAAATGGCTACACACAGTCCCTGAT
 GCTTGCCGCATGGCTGAAATCCAACTACTACAGACTTTGTGATAAGGCTGAAGCTTGGGGCATCGTCCATAGA
 AACGGTGCCACAGCCGGGGTTGTGACCTCGGTGGCTTCCTCTCACTCTCCCGATCCTCGTCTGCAAGGTGC
 AGGACTCCAAACAGGCGAAAAATGCTGCTACTCAGTTCTCTCTCTCTGGTGTGTTGGGCATCTTTGGCCCTC
 ACCTTCGCTTTCATCATCGGACTGGACGGGAGCACAGGGCCCAACGCTTCTCTCTTTGGGATCCTCTTTTC
 CATCTGCTTCTCTGCTGCTGGCTCAAGCTGTCTAGTCTGACCAAGCTCGTCCGGGGGAGGAAGCCCTTTCC
 TGTGGTGATCTCTGGCTCTGGCCGTGGGCTTCAGCCTAGTCCAGGATGTTATGCTATTGAATATATTGTCTGTG
 ACCATGAATAGGAACCAACGTCATGTCTTTCTGAGCTTTCCGCTCCTCGTGCATTAAGAGCTTTGTCTCTCT
 GCTCACTACGCTCCTCTCTCTGATGGGCTGACCTTCTCATGTCTCTCTCACCTTCGTGTGCTTCTCTCACAG
 GCTGGAAGAGACATGGGGCCACATCTACCTCACGATGCTCTCTCATTTGCCATCTGGGTGGCTGGATCACC
 CTGCTCATGCTCTCTGACTTTGACCGGAGGTGGGATGACACCATCTCTCAGTCCGCTTGGGTGCCAATGGCTG
 GGTGTTCTGTGTTGGCTTATGTAGTCCCGAGTTTTGCTGCTCACAAAGCAACGAACCCCAATGGATTATCTCG
 TTGAGGATGCTTTCTCTAACTCACTCTGTAAGAGAGCTATGGTGTGGAGAACAGAGCTTCTCTCAAGAG
 GAATTCATCAAGCTTTTGAAGNACAGGGGACACGCTCTATGCCCTATTCCACACATTTTCAGCTGACAGAA
 CCAGCTCCCCAAAAGGAATTCCTCATCCCACGGGCCACGCTTGGCCGAGCCCTACAAAGACTATGAATAA
 AGAAAGAGGGGAGCTAACTCTGTCTCTGAGAGTGGGACAAATGCAGCCGGGGGAGATCTAGCGGGAGCTCAA
 AGGATGTGGGCAAACTTGTGCTCTCTGAGAAACTGTACAAAGACACTACGGGAACAGTTTGGCTCCCTCCC
 AGCCTCAACCAATTTCTTCATGCTGGGCTGATGTGGGCTAGTAAGACTCCAGTCTTCTAGAGGCGCTGTACT
 ATTTTTTTTTTTTGTCTCATCTTTAGATACTTCTTTAAGTGGGAGTCTCAG

71/162

FIGURE 65

TCATTCCATTAAACATAATTTCTAAATAATAGTAAGTGGTACTAACAAAATAAATAAATTTAATAGCCCTTAGA
AATAAATGACTGTATACTTATACAGGTTGAKMAAAACTCGGTAGGAATAGTTACCTTTTTTGTACTAATGTT
GGTTTCAAAAATACTCAGATTCAATTTIAGTTGGCTGACATCTGGAAGTAGTTAACBACTAACCCAGTGGACTTCA
ACATTCATTTGCTCCAGGCTTCCCCACATCTCACCTCACCACATATCCTGCTATATCCACACAAACAAA
TATTAATATTTGAAATAGCCCATTTGCCGTGAGAAATGACACACAGCTAAAAATACATGCAAGGGTACTTAATGGAG
CCAAACCATGCTCTATACCTAAGGAGAAAAACATGGACATGTAGAAATGCTTTTATTCATGTATTCAAATCAGAA
CAAAATCGATTATATCACTAGACATCAGATGGAGGATACACACAGAAAGTGATACAGATCAGGGTTCACTTTCTC
TTACCCCTCTCTCTGTTAGGACCACTTCCTATTTTAGCCAAATGTTTCTGGTACGGGCCATCTTTCACCCATAA
ATGGCATTTATGTTTCAATGGCTAAAGCTTATTTATGGGTATGGCTCAAGGAGTAAACCCCAATTCACAGAGAT
GTGGCTTTTCTAAAGAACCAATTAAGGGAAATCTTAGTATCTACAACTAAAGTATTAGTCATTCTGAGGATTA
TTTGTTCCTTTAGTATTAGTCTCCTACTACATCCATAACACCTTACTTACTAATTTTATTACACACAACTTT
TCAGAAATTCGTATTTTATTTGAAGGGAGGTACCTGTCTACTTTTCTACAAATAAAACAAAGGGTATTGGCTT
TCTCTAATCCATGCCAACTTCAAAATTCATTCGGGAGTCTTACTACTACTAACAGTGGGATGAACAAABCTAAGAA
AGTACTTCCCTCCACATGTGAATGTTTTAAAAAAGTTTTTGCATAAACCTAAGTGTAAATTTAGCATACCAC
AGTGCTCTGAAGATGGGTCAATPGACGATGTACCATTTGTATATAGGTAATACACATGTAAATCCTAATTTGTTA
ATTAATATATAAGAAATAGGTTTTATCTTTTTANNAAAAAACAAAAAGGTGACCTCCTTCTCAATTCTGTTT
TGTGTATTGCGTCCAAAAGTTGTGTAAATTTTTTAGGTCCAGAAATGTAAAGAAATTTGTTGGAAATACC
TGAAATTTCTGAAAAAAATAAAATAAAATAGATTTTGTACTT

[illegible]

75/162

FIGURE 69

CAGGDCCTCTGAGGCTCCCTTGCGAGGGGCCCGAGCTGCAGGGACAGTGAAGTAGTAGTCCCTTGGGCATCCCG
 CTCTGGGCAGGTCACCAATAGGTCCCGCAGTTCCCAATGGAACTGTTCCAGTCTCTCCCGAGGCTTCCACTT
 CAACCTCTCTCTGTGTCTGCGCAGGCGCTGGAGTTGTGTGACCTTCCCGACCGCTTGGCGCTTCCCAATGGGGGCTGG
 CCTTTTCTCGGGTGGGGGACCTGCTGCTGCCCGGCTGGCTGGCGCTGTGTGTGAGGACTTGGCGCTCTTCTGCAAG
 AGGCTGGGTGCCCTGATGAGTGGACTCTTGTTGCTCTTTTGGGGGTTCCCGCGCTTGTTCGCCAGGTCTCCCTGG
 TGGCTGCTGGCCACAGTCAAGTACGCTGAGCTCGAGCCAGGAAGATCCTGTGCGCTTTGCAGAAAGCCAGTGGCGTGG
 CCCCGGGGACAGTTCCTTGGAGGGAACCTCCCTGGCTACAGAGCTGACCATGCTGTCTTGCACGGAGCCCGCAGC
 CCGGTACCACTCCCACTGGGGCTTCTGCGTACCCGAGTACCTGGAGAAACGGGCTATCTTGGGCTTCAAG
 TCGCTGTTGTTGGTGGAGGCTCAGAGCTAGCTTCCSCCGCAGCCTGGACCTCAGGTGCCACCTTCTACCTGCC
 CTACTTCTGGAGGGCGGGCTGGAGGCGGCAGCGTTGGTCTTCTGCTCTGACCGGAGATTGCTGTGGACGCC
 GCGCTGCTGCTGCTGGGACCAATGGTCAACAGGCTCGCATCCCTGCTGCTCTGCTGGGGCCCAATATCTG
 CCAGGCTGGAGCTGTGCTGTTCTCTCTCTGCTCTGGGGCTCCTGGCTCCCGGGCTGTGTCCGACTCAGAGGCT
 CTTCGAGCGCGAGGCTTTCCCAAGGTGATCAGGGGGCGGGGCTGGGCTTGGTCTGGGGCGGGGTTCTCTGG
 GCCAGGACGCCGGGCCCTTGGACACCTGCAAGCGCGCGCAGGGCTTCTTCTGCAACAGTCTGCTCTGCGCTCC
 CTGCTGCTCTTCCCTGCGTGTGTCTGCTGCTGCTGAGAGCCGAGCGGGGGCTGCCCCAGTCACTGCA
 GGAAGCCGAGCGGCTGCGCGCTCCCACTCTTCCGGGGCGGGCCCGCAGGACCACTGCTCTCTGCTGCGCGC
 CCTCCAACTCTTACTGGGCGGGCCACACCCCGAGCAGCACTAGTCTGCTGCTGGGCTTGGAGGCCAGGATG
 GGACCAAGTCAAGGCTTGGGGCATGGCTGAGTACCCAGGCTCTGGTCCAGGGCAGACATCTCTCTCAGA
 AGCCCTCTCTCAGTGCAGGCTGGAGCGTGGGGACAGCGTGAAGTGTCTCCAGCCAGGCGCCAGGCATGGGA
 GGGCTCTGGGTCTCCCCACGCCACCCAGTAGGTGTGGAGGATAAAGGCTTCTGTGGAACCTTGGGCTCTCTCC
 TGGTCTCTCCCTCAGGCCACAGCTGGGGCTGGAAGGCTCTCAGCTGTGCTGCTCTCCCACTCTGGGGCTCAGC
 AGCAGGAGCCAGGCTGTGAGCGGCTGCTCATAGCCCTGTCTCAGGTAGTGGAGCCCGGGCGGCTCTCTGC
 CCCAGCCAGCAGGTTGCTATGGGGCTTGGCCCTCAGGTCCCTGCCAGCCAGGCTCACTGGGCGCATCCCG
 CTATGGTCACTGTGGCACTGGGCGGCCCTCTCTCATGAAAGAGACTAGCAG

77/162

FIGURE 71

GCGCTTCAGAGATCTGCAGCTGGGATCAGAGTTGTTCTTTTGTGAATCAACTCAGCTCTGCCAGGCCAGCATCTT
 GCTPAGGGGTTACAAATATAATGCCATTTGAACAGTCGCACTGTCATGGAAAAAGGTGAGAGCTTTGTACAGCG
 CGGTGCTCAAGGAGCTGGTGGGAGTTTTTGCAGTTTGTTCACACTTGATTAAGAGGGCTCTGGATCCTTTACAGCC
 TAAATGAATTTACTAGATGAATTTATCAAGGAAACAGAAAGAGAGATTTATGGCAAGAGCTGAGAGATTTATTTGACAC
 GATGTCTTTGTAGAAAGGCCAGCTGGATCTGGTGGCAGGTAGTGGAAAGCCCGGGGTGAAGACAAATTTGGAAACCGA
 ACTGCTCAAAATAGCAGAAAGACATAGAAATTAATTTATGCAATTTCATCTGTGATTCTTGTTCTGTGTCGTG
 TAATAATGAAAGTGAAGACTACAGAGGCCCTACTGGATTTGTATTATATATTAATGGTATTTTATATGCTATTA
 CTTAGCTCTGACAGAAACTACAGAGTTCTATTTCAGGATTTCTGTGTTTACCTGGTGGGAGAAAGGCGCTGCCCTGC
 CAAAGAGACACAGCAAGAGACAGCGCTTTGCTATGTTTACTAAGGAGAGGCTGAGAGACTAAGACAGGTCGACAGG
 TATGTCGGCTTTGGCGCTTCCATCAAGCTTTATATTGCTTTGATTATGATTGAGGAAAGTGGAGAAATTAAGA
 GATGCTTACTTGGTGGCTTCATTAATTAATATATCAAGAAAGAGAGGGAGAAAGATTTCTTAGTTGTCT
 CTTCACCTGGAATACAACTTCATCAAAATGATCCAGGACCTTAAAAAACCAGTTACAGGATTAACAAAGT
 CTTGATGGTATACATTGCGAATTAATTTTACAGAGCTTGGAAAAAGGCTTCAGGGAATATCTGGAGCGGAT
 GAAATGATTTGCATCAGGACTTCATGTTCCAGGGATACACCTCCAGGGATACACCTCCAGGAGGTCCTCCAGTCTCATTTCCAAAGT
 CGGGAGGCTTCAGGTTACTTTTACCTTCAACCTCAAAAGAAAGTTCCGAGGAGTGGAAAGACTGGCTTTATAGATT
 ATAGCCCTATCTTTGGAGAGGATTAAGAGGCCCAAACTCTGAAGTTCGATCAATCTGCATTTGTTGTTGTTGTT
 GAAGCTTTCTCTATTAGGGATCCAAACCTTCATGCTTTGAAATGGATAGAGATTCAGAAACAGTTTGAAGA
 GCTCTATAGCTTTTGAAGATATCTTACCCGATGGTCCGTTCCACAGGATCTGTGGCTTTGTAAATGATATTC
 CTAGACTAGGGAAAGTATGCCCGGACCATTCATTGACCTTCAGAGAAGGTGACTGGGAGCTGGCAATTC
 GACAGGAGCTCAGCTGATGTTCTGTTCTGCTCTTAAGTGTCTGCCAATGATTTTGGAGACCAACTCAGGCCA
 CCATTTGTFAGAGCAGCTGTTCCAGCTCTCAGATACAGCTCCACGCAATTCGGAGAAAGTGAAGGTATGCTT
 TTGTGACATGCTGTTTGAAGTCAAGCTGTAGGGGCTGCTAAGTTTGGAAATATGTCCTCATGGAGCAACT
 CTGCTTCCTGTGGAATCTGATTTCTGAGCTGTGCTCTCGGCGCTGGTGAGCTCATCTTTAATTCCTTCTGCTGCC
 TGTGAATCAGCTGGAGGAGGCTGTGGTGCAGAGGCTGTGCTCAGCCGGTGCAGATGAACACAGCGCGCTGCCAGGA
 GGTTCATACATACCGCCACAGAACACACCGGCTGCAACACATAGCAAAAGCTGATTCACGTTTCTGCTATTTCG
 TTAATGCTGTATCCAGAGGAGCTGAGAGAGGCTCCAGAGGACGAGGAGGAGAGGAGCGAGAGGAGAGAGGA
 GATGTGACTGCTCTGGACAAACACTGTCAATAAACGATGTTGCATGCTGCGAGGCTTACTAGAAATCATTTG
 TGAATCTCTGGAAAGATTTGACAGAACTATGGAAATTAATAAGAGGCCAAACTTTTACGATTAACAGATTT
 GCGCTCTGCTCCAGAGTATCTGAAAGTATTTAAGGATGATGCTGCAAGATCCCTTTATTCATGCTAATGTC
 CTTTATGCGCGGCTCTGCTGTCCGCCCATTCAGCTGTGGTGTGATTTCCACCGTGAGTAGCGCGGAGGAGGGCG
 CTTGTGACAGAGCTACTGCACTTTGTGGATTGCTCTGCTCTGGGGGACAGGTGGGGACACTTCTGAGGCTT
 GTTCACACCTGGCTGCCACAGAGCATGCCAGGCGAGAGCAACACAGCTCTTAAAGGTAGGGTGCAAGTCCA
 TGTACACAGCCCGCTGCAAACTGAATGGCAATGGCTCAATTGAGTATCTGCTGACTCTCCTCAAGAAACCGCG
 AGTGTCTGCTCTCTGCTCCTCGGAAGAACTTACCATCTTTTGAAGGCCCTTGAAGCTCAGAGGCACTGTG
 GATCTCACTTCTGCAAGACCGGGTGGGAGCTCTGGGCTTCAGTGAAGCAGCTGCCCGGAGGCTTTGGTCT
 CCACTCTGCGCTGAGCACTCATCTCTCAGCACAAGTTCTGCTCAGAGAGGAGAGGTGTATTGTCCATTTTGGAG
 AACTGAGCTTTTGGTGTGAAGACAAATTTTATCTTTTATCAAGATCAAGAAAGAGACTACTCGAAGCTTCAAT
 AGGGCTCACTTATCAGCAATATCCAGACCTACCTGACTGTGTGAAGATGTGTGATGGTGAAGGCTTGGTGA
 CCAACAGTTTCAAGTGCACACTCTTACAGCGGAGCTTGGATCATGCAACAGTGTGAGGAGATTTTTTATGGTT
 CATTACTTCTGCACTCTGAAAGGATTAAGTGAAGTCTCTTGTGATCAGAAACAGTTCAGATGAAGAGT
 GAGTACTGTTTGGACAGCTCCGAAAGTATTTAGAAATGTGGATGTATTGACAGGAGCTTCAAGAGAGCA
 GCCGGAGAGAGGCGTGGGCTGCTTATCTGTTCAGAGGCGCTTCTGATGAGTTCATTTATGCTGTTCACTCTC
 GGCACACAGACAGCCCTGTGCAAGCGGGGTACTTTCTACTCTGATCGCTGGGCTTGGGTGAGTGAATAGTCTC
 CAGCTACGGAGGCTTTCTGAGTGAAGAGGCTTACCCCTCCAGAGCATCTTCTGATGCTTCAGCATTTTCAAG
 GTGTTTATAGGAATTAATTAAGAGTCTTCAGATGGGCTCAGGCTCATTTTGAATGATTAAGGACTGTGTGG
 CTCTATATGATTTAGAGGCTTGTGTGCTCAGGCTGCTGCTCATTTATCTGCTGTTATTAATCCAGGATAA
 CTTAAAGGCTCAAAAGTGGGGAGGTTGAGCGACTGTTACAGAAATCAAGAGCATTCATGGAATTAAGTT
 GGAAGAGATAGCTTGAAGATTTCTCTAGATCATCATCAAGAGCTCTGGGAGCATTTTGAATTAAGT
 CAAGCGACATCTCCAGACATGAAGGCG

78/162

FIGURE 72

TCCAAACCBASATTTTCACCGCTATGCCTCCTTTCACCTCTGGGAGTCTTCCAGAGTCTTGCACTCGGGAGAGCAT
GCTCAGGTTTCCCCAGCTCTACAAATTCACCCAGAAATGCCAARGACTTCACAGCTGACCCAGTGGCTCATGGCACTG
CCCTGTGATTTGGTTGAAAATNTTGTTTACACGTATGTTCTTGTCTACTGATTTTCAGAAAGCTGGTTTTGAGACT
GCAGCTTGGACTTAANTTCAGTCACTGGCTGCTCTGGGAGGCATGCTGACCACTCTGGTGTCTCTTTGGCATCTA
CTCAGCCATCTGGTCCACCTTCTCATTTGCCCAAAATATGAGAGGACAGAGAATGGTACCGGTACTGCCAATG
GAGATGGAGGAAGGAGACAGGAAGAAACAGAGGCCAGACCTAGGGACACCCAGCATTTGCAGAAATGGATBAAC
AGCCTTCTTCTAACAAAGGAAGCACAGCAACTGTGATCTGTGAGCTGTGCACACTTCTGGTGGGATTAATTTCT
GGTTTCTACTTCTCTTTTGAAGAGTGGCATGGAGAGTGAACAGCTGCTGCCCCACCACCTGGCATCACAGCCC
CAGAACTCAGCTATTTCCATGGGACCAAGCATCTCATCTCTGGGCTGAGCCAGAAAGACCCCTACTGAGTCC
AGAGGCACTTTTCTGAAGGGCTCTGCTTTGACCTGAGTATTTTATCTATCCTCAGTCTCAGGACCTCTGTTGAT
AGGATTAAGGCCAAGCAGCTCTGCAGAAAGAGCATTTGCTGGAGGAGGTGCAAGAGCTGGGAACCAAGTCTCCA
GTCCCTGGGAAAGCAGTGGTATGGAARAGCAATGGAAAGAGCAATTTGAAAATGCCATTCACCTGTTTCTGGC
CTTTATGATTTCTGCTGAGAAATCCACTGTTAGTCTGATGGGTCTCCTTCATAGCACCAATGACCTGAGAGGC
CTTGTGAGGAAGACTCCATCTGATGACTCAGAGCAGTATTTTTAGTGTGTTATTGTTATTAGCAGAAAGA
GGGCCATAAATACATGGGGCAGCTGATATATCTTAGGCAGAGAGAAATATTCAAATCTTATGTTAT
TTATCTAATATTTATCTCTTTTGTGTGTGACTTATATGTGTGTTATTAATAAAGTAAATTAACAT
GTACTTT

FIGURE 73

CATTCOCACCCCTTCCTTCCTTTAATAAGCAGGAGCGRAAAGACAAATTCCAAAGAGGATTGTTCACTTCAGGG
 NATGANGAATTCAGAAATAATTTTGGTAAATGGATTCCCAATATPCGGGAATAGAAATPAGCTGACACAGTTGACCTG
 CTTTGAAGAAACATACCTGTCCATTTTGTCTAARATATCTATACCAACCAAGCCAAATCAAATGAATTTACACATT
 ATTTTCCACAGTTGAAATGATTGAGTCCACTCTAATTTCTCAGAGAGAATGCCAGCCTCTGGCTTTTGAAA
 ATGATGATTGTCTATCTGCCCTTGGCCATGATATTTACCTTAGCTCTTGCTTATGGAGCTGTGATCTCTTGCT
 GTCTCTGGAAACCTGGCCTGTATCATATCATCTTGAACAACAAAGAGATGAGAAATGTTACCAACCTTCCTGAT
 TGTGAACCTTTCCTTCTCAGACTTGCTTGTTCCTCATGTGTCTTCCCTTTACATTTGTCTACACATTAATGG
 ACCACTGGGTCTTTGGTGAGGCGATGTGTAACTTGAATCCTTTTGTGCATGTGTGTTCAATCACTGTGTCCATT
 TTCTCTCTGGTTCTCATTTGCTGTGGAAACGACATCAGCTGATTAATCAACCCCTCGAGGGTGGAGACCAATATATAG
 ACATGCTTATGTAGGTATTTGCTGTGATTTGGGTCCCTGCTGTGGCTTCTTCTTTGCTTTTCCTGATCTACCAAG
 TAATGACTGATGAGCCGTTCCAAATGTAACCTTGATGCGGTACAAGACAAATACGTGTGCTTTGATCAATTT
 ATTTATTTGCTACTTCAGATATATATACCGCTAAAGAGAGAAACACATCATGTGGACAGATGAGAGACATA
 AGTACAGGTCCAGTGAACCAAAAGAAATCAATATCATGTGCTCTCCATTGTGGTAGCATTTCAGCTCTGCTGG
 CTCCCTCTTACCATCTTAAACACTGTGTTTGATTTGAATCATCBGATCAATGCTACCTCCACCCAAATCTGTT
 ATTCCTGCTCTGCCACCTCAGCAGATGATATCCACTTGTGTCAACCCCATATTTTGTGGGTTCCTGACAAAA
 ACTTCCAGAGAGACTTCGAGTCTCTCTTCAACTTTTGTGATTTCCGGTCTCGGAGATGATGATGTAACAAATA
 GCCATGTCCACGATGACACAGATGTTCCAAACCTTCTTTGAAGCAAGCAAGCCAGTCCGATTTAAAAAAT
 CACACACATGATGATAATGAAAAATCTGAAGACTACTTATAGCCATATGTTCCCGGATGACATCGTTTAAAAA
 CAGCCACACCTGCAACATACTTTGATTACCTGTTCTCCCAAGGAATGGGGTGAATCAATTTGAAATGACTA
 AGATTTTCTGTCTTGTCTTTTACTGCTTTTGTGTAGTTGTCTAATATTACBTTTGGAAACAAAGGTGTGGCT
 TTGGGGTCTCTCGGAATAGTTTTGACCAGACATCTTTGAGGTGCTTTTGTGAATTTATGCATTAATATATAA
 GACTTTTATACGTACTTATTTGAATGAAATTTCTTTAAAGTATTACGATGCGCTGACTTCAGAGTACCTGCC
 ATCCCAATACGGTCAATAGATTGGGTCACTCTGATTAGATTAGATTAGATTAGATTGTCACACAGATTTGGCCATC
 CTTACTTATGATAGGCATCATTTTGTGTGTTACAAATAGTAAACGATGTCBAACAGACGATTCAGAGGCGGA
 AGTACTCTTGAAGTCAATCAGAGAGTGGTTGAGGTTTCTGTTTGTGTTGGTGGTTTGGTTTGGTTTGT
 TTCACCTTAAAGGAGGCTTTCATTTCTCTCCGACGTGATTTGTCATTAATCAAAATTTAAATGATTAAG
 ACATACTCTCTGCTGCAATATATGAGAAATTTGGGACCCACAGGAATGAAGAGAGAAAGCAGCTCCCAAC
 TTCAAACCAATTTTGTACTGACCAACAGAGACTTTTAGAGTAATTAATTTAATTAAGTAAATGATTTGCT
 TTGTCAAGCTTCTGGCTAATATGATTTGAAATGATGTCAGAGATTTCCATTTTTCAGACTGTTCACTGT
 CCATACAGCAGTGCTATATAGTACTGATTTTAACTTTCAATGCTCATCTTTCAGAGGAGTAAACCAAGGT
 ACAATGTTAAAGGAATTTTCACTTTACCTAGCGGGAAAAATACAAAAAAGTGCAGATCTCATATAGCCCCA
 TTTTAACTTGTATAAATCTGTGTGATTTGTGGGCTCTTAATAATATGCACTGTAAGAGTACTGAATGATTTGT
 TTAAGGACAGACATACTTCAATGTATTAACAGATTAAGTATACATGTTTTGATTTTAAAGGCGGAGC
 TTTTAAATTAATCAATATTTGTTTTGCTTTTCTGAGGAGCTCTTTCAGTTTCATTTTCTCATCCATGAC
 TTCCTCCGATGGT

